Controlling for non-inhibitory processes in response inhibition research

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Summary

Central to human adaptive behaviour is the ability to update one's motor actions in the face of environmental changes, for which a key component is the ability to inhibit ongoing actions that are no longer appropriate. A substantial body of previous research has implicated the right inferior frontal gyrus (rIFG) and the pre-supplementary motor area (pre-SMA) as plausible sources of inhibitory control, but it remains unclear whether these regions host a specialised inhibitory control mechanism or instead support a more general system of action updating. This uncertainty stems from the limited number of studies that have controlled for non-inhibitory processes in response inhibition research. The overarching aim of this thesis was to resolve this ambiguity by studying behaviour, neurophysiology and neurochemistry during action updating in the presence and absence of inhibition. For the key experiments, detailed methods and hypotheses were pre-registered prior to data collection to minimise research bias and ensure transparent discrimination of confirmatory and exploratory inferences.

In Study 1, functional magnetic resonance imaging (fMRI) and novel analytic techniques revealed cortical specificity in rIFG associated with response inhibition. Importantly, this right lateralisation continued downstream to subcortical loci and activity in the basal ganglia were found to conform to the functional architecture of the direct, indirect and hyperdirect pathways theorised to underlie response execution and response inhibition. In Study 2, these findings were partially replicated; however, while rIFG was found to mediate pre-SMA and subcortical activity during response inhibition, disruption of this region using offline transcranial magnetic stimulation did not significantly influence either local or remote activity measured subsequently with fMRI or the latency of response inhibition. Furthermore, no relationships between regional activity, behavioural measures of action updating and the concentration of inhibitory neurotransmitter γ-aminobutyric acid (as measured with magnetic resonance spectroscopy) were found. In Study 3, I explored the possibility that differences in the task demands associated with inhibitory and non-inhibitory action updating could explain the differential patterns of activity under various response conditions. Self-report measures indicated that the requirement to inhibit a response was more difficult and frustrating than the requirement to add to an ongoing action plan. As a potential solution, I propose a new paradigm in Study 4 that aims to better control for non-inhibitory processes, while also providing a direct measure of the latency of the stop

process. In conclusion, these findings largely support the potential for a specialised inhibitory control network, but highlight the need for superior control over non-inhibitory processes and task demands.

DECLARATION

This work has not been submitted in substance for any other degree or award at this or any other university or place of learning, nor is being submitted concurrently in candidature for any degree or other award.

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This thesis is being submitted in partial fulfillment of the requirements for the degree of PhD

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Contents

Glossary

ACC	anterior cingulate cortex
ADHD	attention-deficit hyperactivity disorder
AdjMT	adjusted motor threshold
APP	appendix
BF	bayes factor
BG	basal ganglia
BOLD	blood oxygen level dependent signal
Cr	creatine
CT	comfort threshold
cTBS	continuous theta burst stimulation
DA	dopamine
DBS	deep brain stimulation
DLPFC	dorsolateral prefrontal cortex
DT	double-response task
DRT1	reaction time of the first response on double signal trials
DRT2	the latency of the double response process
DVs	dependent variables
EEG	electroencephalography
fMRI	functional magnetic resonance imaging
FWHM	full width half maximum
GABA	γ -Aminobutyric acid
GPe	globus pallidus extern
GPi	globus pallidus interna
goRT	reaction time to go (no-signal) stimuli
H_0	null hypothesis
H_1	alternative hypothesis
IFC	inferior frontal cortex
IFJ	inferior frontal gyrus

IT	ignore task
ITI	inter-trial interval
JZS	Jeffrey-Zellner-Siow prior
LICI	long interval intracortical inhibition
LRP	lateralised readiness potential
MAD	median absolute difference
MDC	multiple demand cortex
MNI	Montreal Neurological Institute
MRS	magnetic resonance spectroscopy
MSNs	medium spiny neurons
MT	motor threshold
NA	noradrenaline
OCD	obsessive compulsive disorder
PD	Parkinson's disease
pre-SMA	pre-supplementary motor area
PRP	psychological refractory period
rIFG	right inferior frontal gyrus
ROI	region of interest
RT	reaction time
SDRI	selective dopamine reuptake inhibitor
SICI	short interval intracortical inhibition
SMA	supplementary motor area
SN	substantia nigra
SNRI	selective noradrenaline reuptake inhibitor
SOA	stimulus onset asynchrony
SOD	signal onset distance
SSD	stop signal delay
SSRI	selective serotonin reuptake inhibitor
SSRT	stop-signal reaction time

SST	stop-signal task
STN	subthalamic nucleus
STR	striatum
THAL	thalamus
TMS	transcranial magnetic stimulation
VAS	visual analogue scale
5-HT	serotonin
50%SSD	the stop signal delay corresponding to *p*(respond|signal)=.50

Chapter 1. Literature review

The flexible coordination of thoughts and actions is central to human adaptive behaviour (Miller & Cohen, 2001). Complex higher-order cognitive functions are proposed to be implemented and maintained by an overarching executive control system, which modulates subordinate processes as a means to achieve successful goal-directed behaviour (Luria, 1966; Miyake, Friedman, Emerson *et al.*, 2000; Miller & Cohen, 2001). A central facet of this cognitive flexibility is the capacity to update actions following changes in the environment, for which response inhibition is crucial (Aron, 2011; Andrea Bari & Robbins, 2013a; Logan & Cowan, 1984; Miyake et al., 2000; Frederick Verbruggen & Logan, 2008, 2009a). While the term inhibition has many associated definitions (see Figure 1.1), this thesis focuses specifically on motor response inhibition and the cancellation of ongoing manual responses that are no longer required.

The ability to countermand initiated responses is vital for survival. For example, not stopping before crossing a road as a speeding car drives by could otherwise prove fatal. Deficits in response control are characteristic of many psychiatric and neurological disorders, including obsessive compulsive disorder (OCD), attention-deficit-hyperactivity-disorder (ADHD) and Parkinson's disease (PD) (e.g. Obeso, Wilkinson, & Jahanshahi, 2011; Penadés, Catalán, Rubia *et al.*, 2007; Rubia, Russell, Overmeyer *et al.*, 2001). This prevalence is the likely motivation behind the breadth of research committed to pinpointing the locus of inhibitory control in the human brain. However, in doing so, many studies are confounded by the lack of control over non-inhibitory processes (Erika-Florence, Leech, & Hampshire, 2014). The aim of this thesis was to address this issue by investigating the behaviour, neurophysiology and neurochemistry during action updating in both the presence and absence of inhibition. This is essential to establish whether response inhibition is supported by a specific neural mechanism, or is merely semantically, as opposed to neurologically, different from other forms of action updating (Hampshire & Sharp, 2015a, 2015b; Mostofsky & Simmonds, 2008; see also Verbruggen, McLaren, & Chambers, 2014a). Such research is crucial to better understanding the aetiology and manifestation of response control deficits in disease.

The updating of ongoing action plans is implemented at different levels (Aron, 2007). Here, I provide an overview of the relevant literature from behavioural, circuit and systems, and neurochemical domains[1] - which directly relate to the theoretical and methodological approaches employed within this thesis. While response inhibition itself is largely the focus of this review, contributing non-inhibitory processes are discussed. Furthermore, as key studies conducted as part of this thesis were pre-registered prior to data collection I provide an overview of the motivation for doing so. I also present an outline of the use of Bayesian statistical methods that are reported throughout, before concluding with a synopsis of the four studies that are presented within this thesis.

1.1. Response inhibition at the behavioural level

As illustrated in Figure 1.1, 'inhibition' is an umbrella term that can be used to describe the suppression of activity at behavioural, cognitive and biological levels. While this thesis explores numerous branches of inhibition (highlighted in Figure 1.1), the behavioural tasks employed in all studies are expected to measure instances of response inhibition, specifically the cancellation (stopping) of ongoing action plans. Of the most prominently cited, and the focus of this thesis, is the stop-signal task (SST; Logan & Cowan, 1984; Verbruggen & Logan, 2008). I first describe this task before providing an overview of related theoretical and methodological considerations.

[1] Although it is also recognised that there is a likely genetic basis for executive control capabilities (Friedman, Miyake, Young *et al.*, 2008), this is beyond the scope of this thesis.

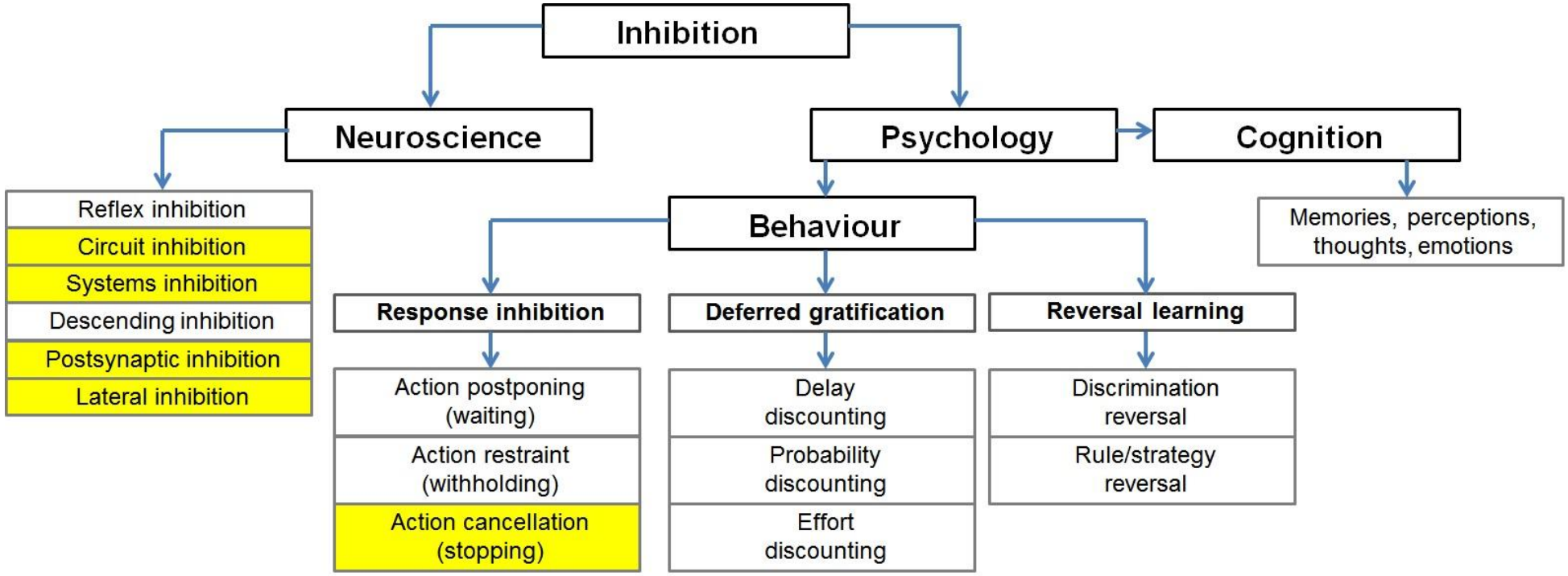

Figure 1.1. The division of definitions of the term 'inhibition' in Psychology and Neuroscience. Terms within Psychology are categorised with respect to behaviour and cognition. Highlighted definitions are those that are explored within this thesis. Image adapted from Aron (2007) and Bari & Robbins (2013a).

1.1.1. The stop-signal task

The SST typically involves a speeded choice reaction time task. Participants are instructed to execute one of two responses as fast and as accurately as possible. When practiced, this allows a prepotent response tendency to develop. On a subset of trials, a signal (either auditory or visual) is presented after a variable delay alerting the participant to withhold (stop) their response (Figure 1.1; Logan & Cowan, 1984). Although the way in which SST is implemented varies across studies, these basic parameters remain consistent.

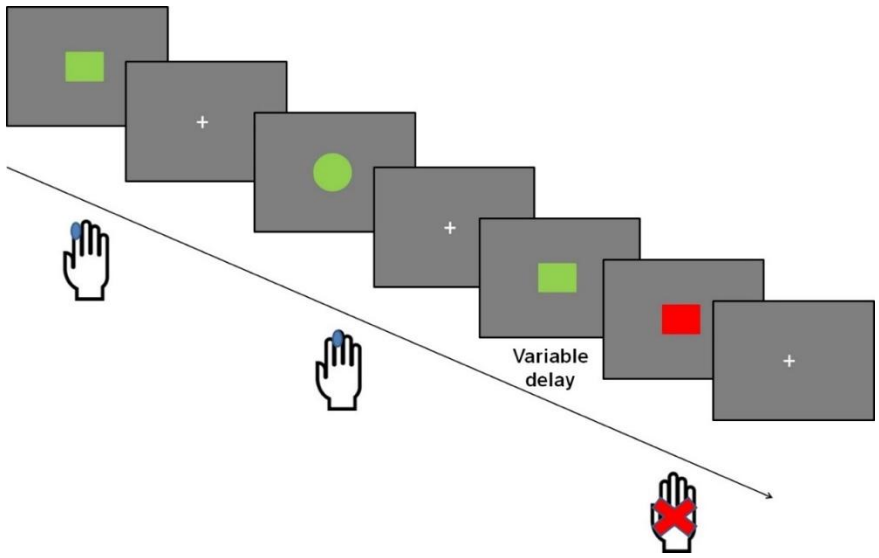

Figure 1.2. An example of three trials as presented in a standard SST. Participants are instructed to identify the shape presented. Here, left finger responses are required upon presentation of a square and right finger responses are required upon presentation of a circle. On a minority of trials (usually 25-33%), a signal is presented (here the green square turns red) after a variable delay, instructing the participant to try to inhibit their response.

Whether or not a response is successfully inhibited is conceptualised as a race between two processes: a go process, which is elicited upon presentation of a go stimulus, and a stop process, which is elicited upon presentation of a stop signal. If the stop process finishes before the go process then a response is successfully inhibited. However, if the go process finishes before the stop process then a response is executed (Figure 1.3). Crucially, the longer the delay between the go stimulus and the stop signal (the stop-signal delay; SSD) the greater the probability of responding (*p*(respond|signal); Figure 1.4, see also Carver, Livesey, & Charles, 2001; Lappin &

Eriksen, 1966). In many studies, the SSD is dynamically adjusted to ensure that the probability of successful inhibition occurs on approximately 50% of stop signal trials (*p*(respond|signal)=.50). This represents the optimum point of competition between the stop and go processes (Logan & Cowan, 1984). This, along with the prepotent tendency to respond to go stimuli and the random presentation of stop-signals, encourages participants to initiate a response that must be cancelled as opposed to simply deciding whether to respond or not (although see Shenoy & Yu, 2011, who claim participants constantly make a decision whether to go or not).

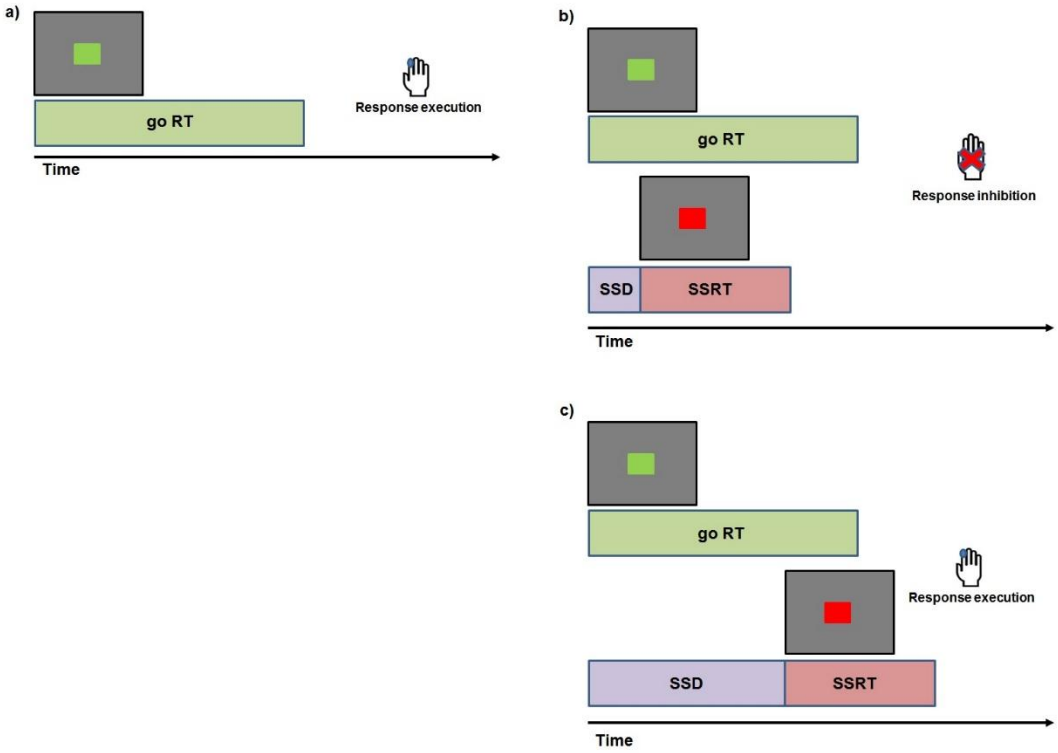

Figure 1.3. The SST conceptualised as a race between stop and go processes (Logan & Cowan, 1984). Here, the go stimulus is represented by the presentation of the green square and the stop-signal represented by the presentation of the red square. The go process is elicited as soon as the go stimulus is presented. The go reaction time (RT) represents the time it takes for a response to be executed. The stop process is elicited as soon as the stop signal is presented. The time the stop process takes to complete is the stop-signal RT (SSRT). **(a)** illustrates the execution of a response when only a go stimulus is presented; **(b)** and **(c)** illustrate the race between processes upon presentation of a stop signal when the stop-signal delay (SSD) is varied. At short SSDs **(b)** the stop process is likely to finish before the go process and the response is successfully inhibited. At long SSDs **(c)**, the go process finishes before the stop process and a response is executed.

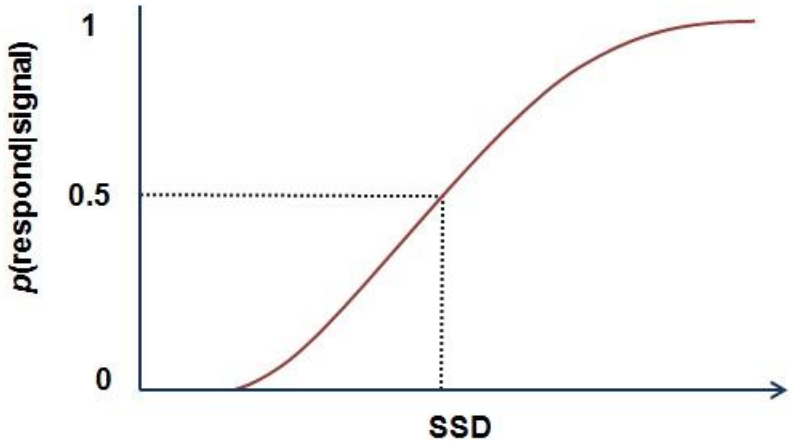

Figure 1.4. A typical inhibition function. As the delay between the stimulus and signal presentation (SSD) increases the probability of responding to a signal trial (*p*(respond|signal) also increases. The dashed line represents the SSD at which *p*(respond|signal) is at 0.5- the theoretical point of optimum competition between the stop and go processes (Logan & Cowan, 1984).

As there is no overt measure of stop-signal reaction time (SSRT) on successful stop signal trials, the latency of this process must be estimated. The independent horse-race model (hereafter referred to as the independent race model; Logan & Cowan, 1984) provides a mathematical basis from which this can be achieved- an advantage the model has over its predecessors (Lappin & Eriksen, 1966; Ollman, 1973; Vince, 1948). To estimate the latency of the stop process, the model makes use of parameters known to the researcher. While the SSD provides the time at which the stop process begins, the time at which the stop process finishes requires the integration between two additional parameters: (1) the go reaction time distribution (goRT; RT to no-signal trials) and (2) *p*(respond|signal). The point in the goRT distribution where the integral matches *p*(respond|signal) provides an estimate of the finishing time of the stop process. SSRT is computed as the SSD subtracted from this finishing time (Figure 1.5, Logan & Cowan, 1984; see also Verbruggen & Logan, 2009b). In actuality there are multiple methods of estimating SSRT which provide more or less robust estimates depending the way in which SSDs are manipulated (Logan & Cowan, 1984; see also Verbruggen, Chambers, & Logan, 2013).

To ensure reliable estimation of SSRT, the model assumes both contextual and stochastic independence. That is, the RT to go trials is unaffected by the presentation of

stop signals and that trial-by-trial variability in goRTs are not affected by trial-by-trial variability in SSRT (Logan & Cowan, 1984). While the independence assumptions are met in the majority of studies (Verbruggen & Logan, 2009b), there is evidence of violations of these assumptions with more complex tasks (Verbruggen & Logan, 2015). These violations and ways to overcome them are explicitly discussed in Chapter 7.

SSRT provides an index of inhibitory control capability. The shorter the SSRT, the more efficient the control (Logan & Cowan, 1984; Verbruggen & Logan, 2009b). SSRT can be used to study inhibitory deficits in clinical populations and differences are often found in patient groups vs. healthy controls. For example, participants with OCD, ADHD and PD, all show prolonged SSRTs (Obeso *et al.,* 2011; Penadés *et al.,* 2007; Rubia *et al.,* 2001). SSRTs are also known to be elongated in participants with impulsive traits, such as those with addictions (Ersche et al., 2012; Fillmore & Rush, 2002). Differences in SSRT are also evident across the lifespan, and are representative of the development and decline of inhibitory control (Bedard, Nicols, Jose *et al.,* 2010; Durston, Tottenham, Thomas *et al.,* 2003; see review Durston & Casey, 2006). SSRT can also be used as a measure of change in inhibitory control over time. For example, improvements in SSRT (i.e. shorter SSRT) are often found in patient groups undergoing therapeutic treatment (e.g. in ADHD: Rubia, Allegria, Cubillo *et al.,* 2014; Vaidya, Austin, Kirkorian *et al.,* 1998). *p*(respond|signal) can also be used as a measure of inhibitory performance that often parallels SSRT, when SSDs are fixed[2]. Groups who exhibit prolonged SSRTs tend to produce more commission errors relative to controls and vice-versa (Logan & Cowan, 1984).

[2] When SSDs are adjusted by a tracking procedure *p*(respond|signal) should be similar across all groups and/or conditions.

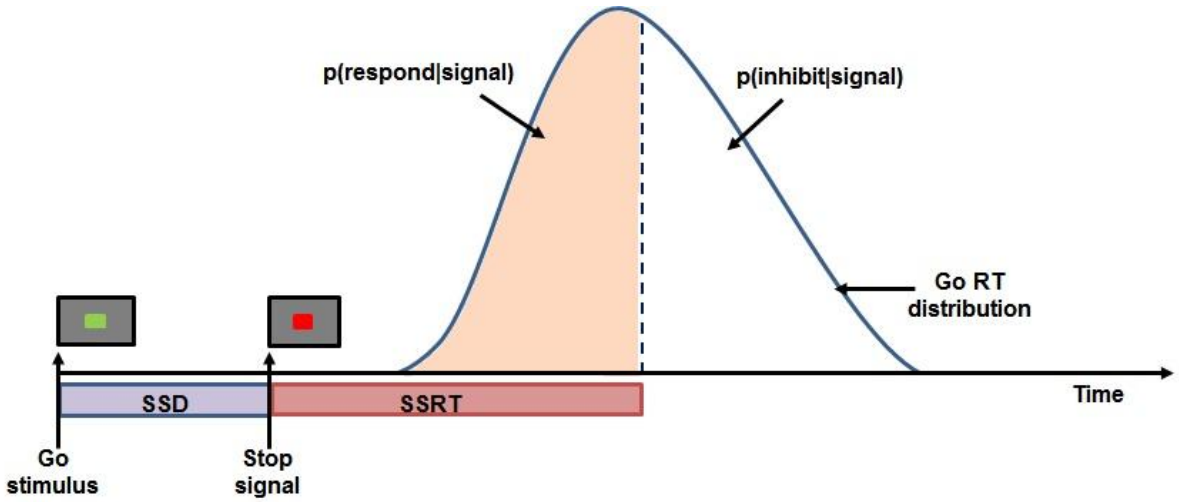

Figure 1.5. Graphic representation of the independent race model (Logan & Cowan, 1984). The probability of incorrectly responding to a stop signal (*p*(respond|signal) is represented by the pink area- that is, under circumstances where the go process is fast enough to evade inhibition. The model assumes that the mean reaction time (RT) to unsuccessfully inhibited stop signal trials is shorter than the than the mean RT to go trials: the former is represented by the mean of those trials that were fast enough to escape inhibition (those responses to the left of the vertical dashed line), whereas the latter is represented by the mean of the entire goRT distribution. The image demonstrates the onset of go and stop processes. **SSD**=stop-signal delay; **SSRT**= stop-signal reaction time. Image adapted from Verbruggen & Logan (2008).

Both SSRT and *p*(respond|signal) provide measures of *reactive* control. That is, the outright stopping of all (global) responses (Aron & Verbruggen, 2008; Frank, 2006; Wiecki & Frank, 2011). Instances of reactive inhibition are proposed to be driven by exogenous stimuli that occur unexpectedly (Aron, 2011; De Jong, Coles, & Logan, 1995; De Jong, Coles, Logan, & Gratton, 1990). This can be distinguished from *proactive* inhibition, which is theorised to occur when there is sufficient time to plan the withholding of actions (Aron & Verbruggen, 2008; Aron, 2011; Braver, 2012; Verbruggen & Logan, 2009c) and can lead to more selective inhibition (when participants are told that they have to inhibit a specific response; Aron & Verbruggen, 2008; De Jong *et al.*, 1990, 1995; Greenhouse, Oldenkamp, & Aron, 2012). These differences are important as proactive and reactive control mechanisms are likely supported by different (but partially overlapping) neural substrates (Aron, 2011). In the SST, proactive control is indexed by goRT. Slowing of goRT is evident in blocks where stop signals are presented relative to those where they are not - even when participants are instructed not to wait for a signal. This is expected to be due to a speed-accuracy tradeoff, where speed of responding to go stimuli is traded in favour of greater stop signal success (although dual-task demands also contribute; see Verbruggen & Logan,

2009c). Reactive strategic adjustments are also evident on a trial-by-trial basis. Participants often slow their responses after an unsuccessful stop signal trial and speed their responses after a successful stop signal trial (Bissett & Logan, 2011, 2012a, 2012b; Verbruggen & Logan, 2009c; Verbruggen, Logan, Liefooghe, & Vandierendonck, 2008). These adjustments are likely adopted as participants try to establish optimum task performance, varying strategies as a means to resolve the conflict between the speed of responding to go trials and the withholding of ongoing actions upon presentation of a stop signal (Verbruggen & Logan, 2009b).

1.1.2. Theoretical and methodological considerations

Classically, response inhibition has been conceived as a distinct executively controlled function (e.g. Miyake *et al.*, 2000). However, as illustrated in Figure 1.1, inhibition is a global concept and likely the product of many combined processes (see Hampshire & Sharp, 2015a, for a review). Although the idea of a single 'homunculus' exerting overall inhibitory control has been refuted (Verbruggen *et al.*, 2014a), the tendency to categorise cognitive processes and localise them within the frontal lobes remains (e.g. Miller & Cohen, 2001; Miyake *et al.*, 2000; Stuss & Alexander, 2007). Such modular views offer simple interpretations, but the extent of overlapping neural networks under different task conditions indicates that multiple processes may be supported by the same regions (Banich & Depue, 2015; Duncan, 2001; Erika-Florence et al., 2014; Hampshire & Sharp, 2015a, 2015b; Hampshire, 2015). In response inhibition research, this oversimplification partly stems from the use of tasks designed to measure response inhibition but not the additional processes required for task completion (Mostofsky & Simmonds, 2008; Verbruggen *et al.*, 2014a).

Clearly, SST performance requires cognitive processes beyond the inhibition of a response- i.e. processes that are non-inhibitory. Participants must engage top-down attentional mechanisms to detect a signal and orient behaviour towards stopping a response (Chatham, Claus, Kim *et al.*, 2012; Chevrier, Noseworthy, & Schachar, 2007; Corbetta, Patel, Shulman, 2008; Corbetta & Shulman, 2002; Leiva, Parmentier, Elchlepp & Verbruggen, 2015; Verbruggen, Stevens, & Chambers, 2014b; Wessel & Aron, 2013). Furthermore, participants are required to distinguish between multiple competing demands associated with the go and stop processes to resolve the conflict between them (Botvinick, Braver, Barch *et al.*, 2001), adjust performance to meet task

demands (i.e. by reactive and proactive strategies discussed above; Verbruggen & Logan, 2008; Verbruggen & Logan, 2009c; Aron, 2011) and maintain response rules within working memory (Barber, Caffo, Pekar & Mostofsky, 2013; Mostofsky *et al.*, 2003). The importance of these non-inhibitory processes have been recently formalised by Verbruggen *et al.* (2014a). They propose that, at a basic level, all actions are the product of 3 distinct processes: (1) signal detection, (2) action selection, and (3) action execution (Figure 1.6). At each stage there is competition (see also Levy & Wagner, 2011). For example, to detect a signal, participants must monitor their environment and suppress all other irrelevant information (Chatham *et al., 2*012; Chevrier *et al., 2*007; Corbetta *et al., 2*008; Corbetta & Shulman, 2002; Leiva *et al., 2*015; Wessel & Aron, 2013; Verbruggen *et al., 2*014b). Verbruggen *et al.* (2014a) postulate that action control is dependent on the collaborative efforts of different processes across time, which enable flexible behavioural change and response automisation (Figure 1.6). Under this framework, response inhibition is conceptually similar to other forms of response control, with the decision to stop a form of response selection (see also Logan, Van Zandt, Verbruggen, & Wagenmakers, 2014; Mostofsky & Simmonds, 2008; Rubia *et al.*, 2001). This conceptual framework highlights the need for research to move beyond simply defining 'what' inhibition is (at a functional level) and to focus on the mechanistic foundations of response control (Verbruggen *et al.*, 2014a).

Conceptualising response inhibition as the result of a convergence of various cognitive processes implies that 'inhibition' itself may not be supported by a specific (single) neural construct. To ascertain this, it is necessary to explore action control in both the presence and absence of inhibition under otherwise identical task conditions to minimise confounding influences from additional, non-inhibitory, cognitive processes. This forms the primary focus of this thesis.

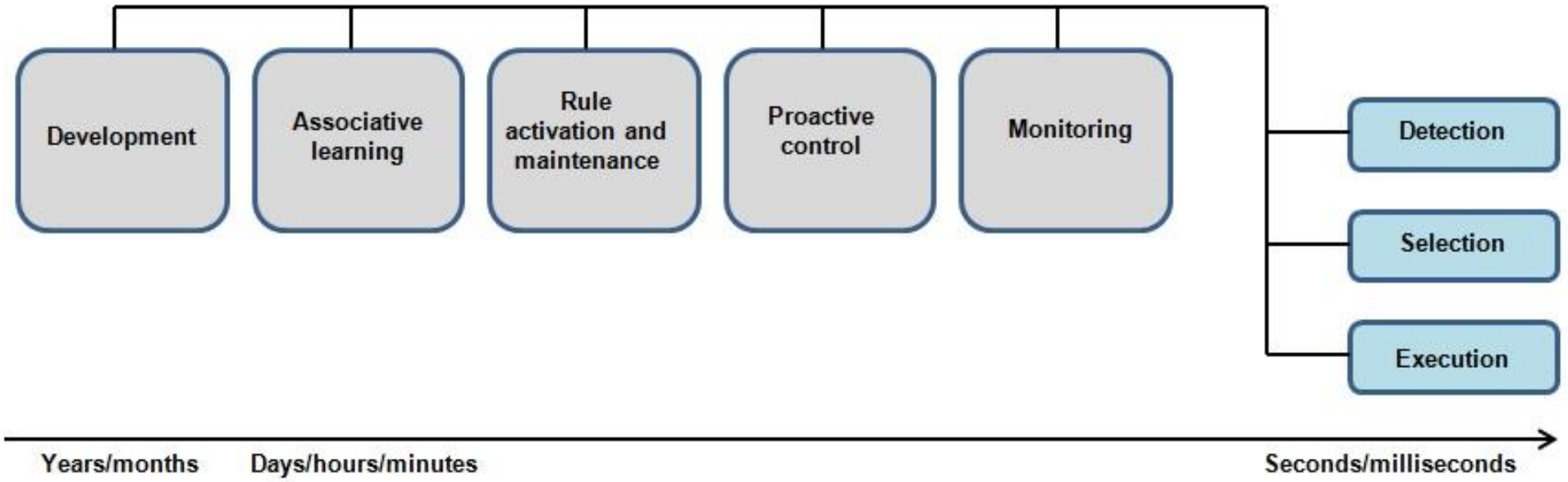

Figure 1.6. Verbruggen *et al.*'s (2014a) conceptual framework of action control. The model proposes that action control is comprised of 3 distinct stages: (1) signal detection; (2) action selection and (3) action execution. Each of these stages can be influenced by additional processes (presented in the grey boxes), which are dominant at different points in time (denoted by the black arrow). These additional processes help to facilitate the acquisition and development of new stimulus-response associations, behavioural change and can ultimately automatise response control.

1.2. Response inhibition at the circuit and systems level

Circuit and systems level inhibition refers to the anatomical and functional neural connectivity between regions that underlie inhibitory control (Aron, 2007). In the motor domain, converging lines of evidence indicate that a specialised inhibitory network involved in stopping actions may originate in either the right inferior frontal gyrus (rIFG) or the pre-supplementary motor area (pre-SMA). The anatomical locations of these regions and mutual projections to one another and to basal ganglia (BG) structures known to be involved in motor responding (Aron, Behrens, Smith *et al.*, 2007; Aron & Poldrack, 2006; Duque, Labruna, Verset, *et al.*, 2012; Forstmann, Keuken, Jahfari *et al.*, 2012; Jahfari, Waldorp, van den Wildenberg *et al.*, 2011; Li, Huang, Constable, & Sinha, 2006; Miller & Cohen, 2001; Zandbelt, Bloemendaal, Neggers *et al.*, 2012) render them ideal candidates as sources of top-down inhibitory control. Both regions are active in imaging studies where participants are required to withhold responses (e.g. Aron *et al., 2*007; Aron & Poldrack, 2006; Buch, Mars, Boorman, & Rushworth, 2010; Garavan, Hester, Murphy *et al.*, 2006; Li *et al.*, 2006; van Belle, Vink, Durston, & Zandbelt, 2014; Wager et al., 2005; Xue, Aron, & Poldrack, 2008; Zandbelt *et al.*, 2012), lead to impaired stopping performance when lesioned (Aron, Fletcher, Bullmore *et al.*, 2003; Floden & Stuss, 2006; Nachev, Wydell, O'Neill *et al.*, 2007; Picton, Stuss, Alexander *et al.*, 2007) or when disrupted with transcranial magnetic stimulation (TMS[3]; Cai, George, Verbruggen *et al.*, 2012; Chambers, Bellgrove, Stokes *et al*., 2006; Chambers, Bellgrove, Gould, *et al.*, 2007; Chen, Muggleton, Tzeng *et al.*, 2009; Dambacher, Sack, Lobbestael *et al.*, 2014; Obeso, Robles, Marrón, & Redolar-Ripoll, 2013; Verbruggen, Aron, Stevens, & Chambers, 2010; see also Hsu, Tseng, Yu *et al.*, 2011), exhibit abnormal activity in clinical groups for which deficits in response control are known (e.g. OCD, ADHD and PD, e.g. Obeso *et al.*, 2011; Penadés *et al.*, 2007; Rubia *et al.*, 2001) and show age related maturation and degeneration consistent with changes in inhibitory control (Durston & Casey, 2006; Schel, Scheres, & Crone, 2014). While there is a wealth of literature proposing these regions support the implementation of response inhibition (see reviews Aron, Robbins, & Poldrack, 2014a; Aron, 2007; Banich & Depue, 2015; Bari & Robbins, 2013a; Calabresi, Picconi, Tozzi *et al.*, 2014; Chambers, Garavan, & Bellgrove, 2009; Jahanshahi, Obeso, Baunez *et al.*, 2014; Stuphorn, 2015), the aim of this section is to review the evidence with respect to

[3] TMS is a neurostimulation technique that induces transient disruptions in cortical excitability via the application of a time-varying magnetic field (commonly referred to as a 'virtual lesion', (Siebner, Hartwigsen, Kassuba, & Rothwell, 2010; Wagner, Rushmore, Eden, & Valero-Cabre, 2009).

alternative interpretations. That is, whether cortical and subcortical regions pinpointed as crucial to the implementation of response inhibtition may instead support processes that are not necessarily inhibitory in nature. Although it is well established that both cortical and subcortical activity act to support motor control, for simplicity I largely focus on individual regions. I begin with an overview of the role of the rIFG, which has received the most research attention, before discussing contributions from the pre-SMA and BG.

1.2.1. The right inferior frontal gyrus

The IFG is situated in the ventrolateral prefrontal cortex and is the collective name for the *pars opercularis*, *pars triangularis* and *pars orbitalis* (corresponding to Brodmann areas 44, 45 and 47, respectively; Figure 1.7). While it has been argued the rIFG specifically implements response inhibition (e.g. Aron, 2011; Aron *et al.*, 2007, 2014a, 2014b; Aron & Poldrack, 2006), alternative interpretations for its role in response inhibition tasks have been offered. Here I focus on the potential for the rIFG to support attentional processes (including the allocation of attention and context monitoring) and the adjustment of action plans to implement goal-directed behaviour. Additionally, I discuss the recent proposal that the rIFG may be part of a multiple demand cortex (MDC; Duncan, 2000, 2001, 2010, 2013; Duncan & Owen, 2000; Fedorenko, Duncan, & Kanwisher, 2013) that acts to supports numerous cognitive processes that contribute to inhibitory control.

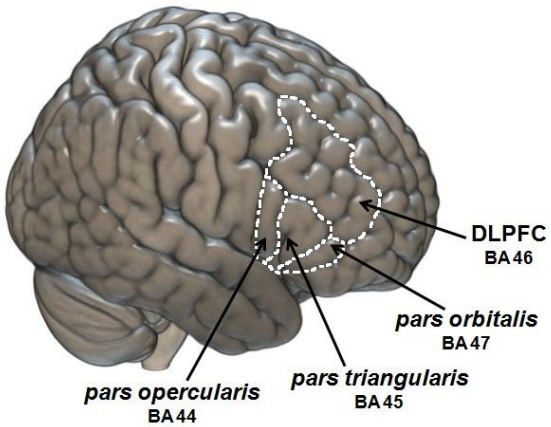

Figure 1.7. The location of the *pars opercularis*, *pars triangularis*, and *pars orbitalis*. Combined these regions form the rIFG. The dorsolateral prefrontal cortex (DLPFC) is also depicted. Corresponding Brodmann's areas (BA) are shown.

The rIFG, context monitoring and attention allocation

Successful SST performance is reliant on attentional mechanisms to quickly and accurately detect a stop signal (Chatham *et al.*, 2012; Chevrier *et al.*, 2007; Corbetta *et al.*, 2008; Corbetta & Shulman, 2002; Leiva *et al.*, 2015; Verbruggen *et al.*, 2014b). The rIFG is activated during target detection, when signals are presented, even when there is no requirement to countermand an ongoing action (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010; Sharp, Bonnelle, De Boissezon *et al.*, 2010[4]). Thus the rIFG may act to support attentional, as opposed to inhibitory, processes required in the SST. This interpretation is consistent with Corbetta *et al.*'s (Corbetta *et al.*, 2008; Corbetta & Shulman, 2002) dorsal vs. ventral model of attention. It is assumed that bottom-up (stimulus-driven) processes are modulated by a ventral frontoparietal pathway involving the right inferior frontal cortex (rIFC), which acts to detect behaviourally-relevant stimuli. Upon identification, information is projected to the temporoparietal junction which acts to interrupt the dorsal pathway to trigger top-down control (although note this remains unverified, see Vossel, Geng, & Fink, 2014, for a review). Accordingly, the rIFC has thus been conceived as an attentional, as well as an inhibitory "circuit breaker", and whether the two are dissociable has been questioned (Chambers *et al.*, 2009; see also Fassbender, Simoes-Franklin, Murphy *et al.*, 2006)

Aron *et al.* (Wessel & Aron, 2013; Aron *et al.*, 2014a) argue that attention and inhibition, although separate processes, are inextricably linked. In a recent study, Wessel & Aron (2013) demonstrated that the EEG (electroencephalogram[5]) signature associated with the presentation of novel auditory stimuli is similar to that generated upon the presentation of signals to be inhibited (see also Mars, Debener, Gladwin *et al.*, 2008). Consequently they argue that the presentation of salient stimuli automatically recruits the inhibiton network even in the absence of outright stopping. They propose this partial 'braking' can be observed in situations where responses that do not require adjustment are elongated upon presentation of a signal (note this may also be the result of capacity sharing; Miller, Ulrich, & Rolke, 2009; Navon & Miller, 2002; Tombu & Jolicœur, 2002, 2003, 2005). However, recent work has also shown that the presentation of infrequent and behaviourally irrelevant stimuli can actually impair no-go performance (Leiva *et al.* 2015), opposing what would be expected if the inhibition

[4] Hampshire *et al.* (2010) instructed participants to count the number of signals presented in a SST with no motor requirements. Sharp *et al.* (2010) instructed participants to continue making a go response upon presentation of a signal as presented in a SST.

[5] A method of detecting neural activity from the cortex beneath the site of electrode placement.

system was already partially recruited. Thus the presentation of salient stimuli is likely to recruit attentional mechanisms involved in stimulus detection as opposed to response inhibition.

Overt attempts at identifying the neural correlates of attentional monitoring and response inhibition have indicated that the rIFG may be functionally subdivided to support both processes. This has been demonstrated using variants of the go/no-go paradigm - a task similar to the SST except that stimulus and signal presentation occurs simultaneously (i.e. there is no delay), signals typically occur on 50% of trials and *p*(inhibit|signal) is much higher. Also note go/no-go tasks are argued to require action restrain rather than action cancellation (see Figure 1.1; Eagle, Bari, & Robbins, 2008). Using this task, Chikazoe, Jimura, Asari *et al.* (2009) demonstrated differential rIFG activity by manipulating the frequency of go stimuli presentation. Infrequent presentation was found to activate the dorsal rIFG (the inferior frontal junction, rIFJ). However, the ventral rIFG was specifically recruited under conditions of response inhibition. Similar divisions have also been observed when participants are required to either ignore or cancel a response upon presentation of a signal in the SST (Cai & Leung, 2011; Cai & Leung, 2011; see also Brass, Derrfuss, & Von Cramon, 2005; Chevrier *et al.*, 2007). Recent meta-analyses also support this functional dissociation, consistently demonstrating the rIFJ to be recruited during target detection, and the ventral rIFG during response inhibition (Cai, Ryali, Chen *et al.*, 2014; Levy & Wagner, 2011; Sebastian *et al.*, 2016[6]). Furthermore, functional connectivity analyses reliably demonstrate the rIFJ and ventral rIFG to be co-activated with regions crucial for attentional and motor control, respectively (see meta-analysis by Sebastian *et al.*, 2016). However, the rIFG is also activated when participants are required to switch, as well as stop, responses (Boecker, Drueke, Vorhold *et al.*, 2011; Mars, Piekema, Coles *et al.*, 2007). Although switching action plans likely involves a degree of stopping, it is possible that the adjustment of an action plan to achieve goal-directed behaviour may also account for this activity. This is discussed in the next section.

[6] Cai *et al.*'s (2014) meta-analysis indicates involvement of the rIFC in implementing motor inhibition, but the detection of behaviourally relevant stimuli argued to be controlled by the right anterior insula as opposed to the rIFJ.

1.2.1.2. The rIFG and the adjustment of action plans to achieve goal-directed behaviour

The context-cueing paradigm employed by Verbruggen *et al.* (2010; see also Verbruggen & Logan, 2009c) provides a means to assess multiple forms of action-updating in the presence and absence of overt response cancellation. The context-cueing paradigm includes three separate tasks- a SST, a dual-task (otherwise referred to as a double-response task; DT) and an ignore task (IT; Figure 1.8). In each task, participants are instructed to respond as fast and as accurately as possible to go stimuli. On a subset of trials (here, 33%) a signal is presented after a variable delay. How participants are to respond to the presence of a signal depends on the task (Figure 1.8). In the IT, participants must ignore the presence of the signal and respond as if there was no signal (i.e. executing a response and running an action plan to completion). In the SST, participants are instructed to withhold their response, and in the DT participants are instructed to execute an additional thumb response. Thus, the SST and DT both involve action updating, with the former requiring updating by inhibiting an existing action plan, and the latter requiring adding a response to an existing action plan. The presence of signals in all 3 tasks controls for potential confounds associated with signal detection.

Verbruggen *et al.* (2010) sought to establish the causal involvement of the rIFJ, rIFG and pre-SMA in the adjustment of ongoing action plans using a variant of TMS that is known to reduce cortical excitability for approximately one hour (continuous theta burst stimulation; Huang, Edwards, Rounis, *et al.*, 2005; Huang, Rothwell, Chen, & Lu, 2011). When applied to either the rIFG or rIFJ, TMS was found to impair updating performance in the SST and DT. Importantly, this impairment was specifically found on signal trials only, where SSRT and DRT2 (the duration between the onset of the signal and onset of the additional response on double-signal trials) were elongated relative to sham (control) stimulation (Figure 1.9)[7]. TMS to the pre-SMA did not exert any influence on subsequent updating behaviour, which may be due to its deep location within the medial wall (Figure 1.14).

[7] The term sham is used to describe the control for continuous theta burst stimulation (cTBS) in which the TMS coil is oriented away from the scalp (usually by 90°). This enables the auditory artefact associated with cTBS application to be maintained, whilst minimising the magnetic flux that reaches the cortex (Lisanby, Gutman, Luber *et al.*, 2001).

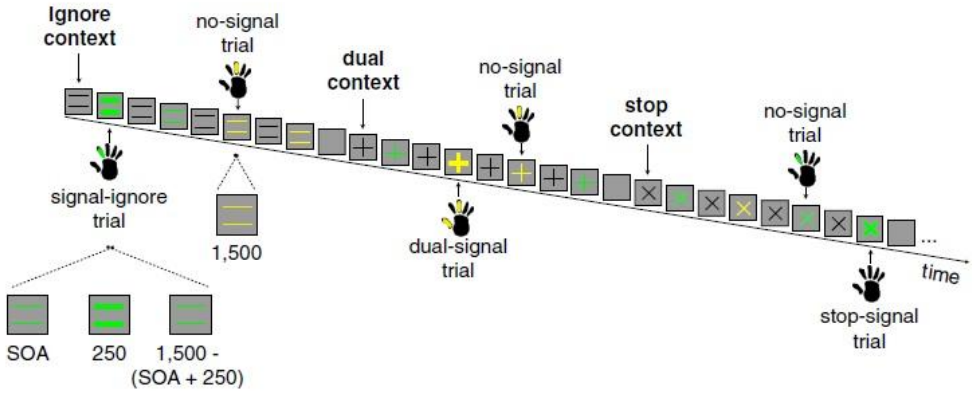

Figure 1.8. The context-cueing paradigm as employed by Verbruggen *et al.* (2010). Left and right digit responses were required upon presentation of green or yellow stimuli (counterbalanced across participants). On 33% of trials, the presentation of a bold stimulus signalled participants to update their responses based on the shape of the stimuli presented. **=** corresponded to the ignore task, **+** corresponded to the dual-task and **X** corresponded to the stop task.

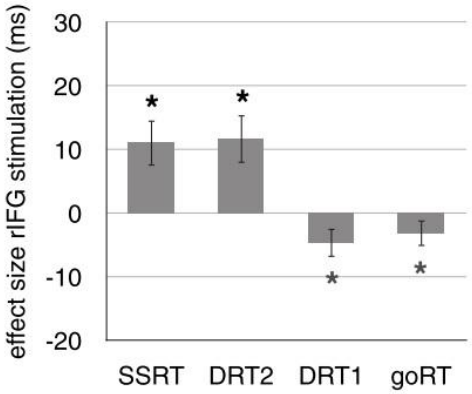

Figure 1.9. TMS-induced modulation of RTs on trials in the SST and DT when applied to the rIFG (image from Verbruggen *et al.,* 2010). SSRT and DRT2 were found to be prolonged after TMS relative to sham (control) stimulation, reflecting impairments in inhibitory and non-inhibitory action updating, respectively. This is in contrast to the decrease in RTs observed for go trials and the initial response on double signal trials (DRT1), where no updating of ongoing action plans was required.

Although these findings suggest roles for the rIFG and rIFJ beyond inhibition, they do not indicate whether impaired performance is the result of disrupted processes involved in the updating of attention or those involved in the updating of an action plan. To differentiate these possibilities, Verbruggen *et al.* (2010) considered their findings with respect to the psychological refractory period (PRP; Pashler, 1994; Telford, 1931; Welford, 1952). In dual-task situations, the PRP is argued to reflect the presence of a

central bottleneck that hinders the selection of a second response while the selection of the primary response is ongoing (Dux, Ivanoff, Asplund, & Marois, 2006; Pashler, 1994; Ruthruff, Pashler, & Hazeltine, 2003; Telford, 1931; Welford, 1952). The presence of the PRP may either reflect a structural constraint preventing the selection of two responses simultaneously, or a strategic serial postponement to ease the speed of processing in multi-task situations (e.g. Logan & Gordon, 2001; Meyer & Kieras, 1995, 1997a, 1997b; Miller *et al.,* 2009; Schumacher & Lauber, 1999; Tombu & Jolicœur, 2003)[8]. It is proposed that for a motor response to be executed in reaction to a stimulus three sequential stages must be undertaken: a perceptual stage (where a stimulus is detected and perceptual processing occurs), a decision stage (where an appropriate motor response is selected) and an execution stage (where the motor response is made)[9]. In situations where two (or more) speeded tasks are carried out concurrently, RT to a second stimulus is significantly slowed by the response to the first. This interference is known as the PRP and is assumed reflect the inability of the decision stages of each task to overlap (Telford, 1931; Welford, 1952). In effect, the decision stage of the first task creates a bottleneck whereby this must be completed before the decision stage for the second task can begin (see Figure 1.10). DRT2 decreases as stimulus onset asynchrony (SOA) increases. This is because the bottleneck is present (and more influential) at short, relative to long, SOAs (see Figure 1.10; Dux *et al.,* 2006; Pashler, 1994; Ruthruff *et al.,* 2003).

Verbruggen *et al.* (2010) argue that if TMS influenced decision making prior to the selection (decision) stage of the second response (during perceptual processing), its effects would be greater at long compared to short SOAs (Figure 1.10a)[10]. This is because at short SOAs, the disruption caused by TMS would be absorbed into the bottleneck (Figure 1.10a). However, if the disruption influenced non-perceptual processes either during or after the bottleneck, any impairment would be consistent across SOAs (Figure 1.10b). An interaction between TMS and SOA on DRT2 was only found when TMS was applied to the rIFJ and not when applied to the rIFG. Thus, this study provides additional (and causal) support for the rIFJ's role in attentional processing, but suggests the ventral rIFG may be involved in updating action plans in a

[8] Although see Fischer & Plessow (2015) who argue that serial and parallel processing methods are not completely independent.

[9] Note that that sequential models of decision making, such as that presented here, are useful to consider in a controlled experimental environment (such as in the SST or DT), but are unlikely to account for real-life encouters, where decision making is more complex (Forstmann, Ratcliff & Wagenmakers, 2016).

[10] This logic and locus of slack procedure has been used elsewhere (e.g. Gilbert, 2005; Johnston, McCann, & Remington, 1995; Mccann & Johnston, 1992).

manner that may not require outright action cancellation (see also Fellows & Farah, 2007; Levy & Wagner, 2011). Consistent with these findings, Dippel & Beste (2015) report impaired execution of response sequences subsequent to TMS to the rIFG[11].

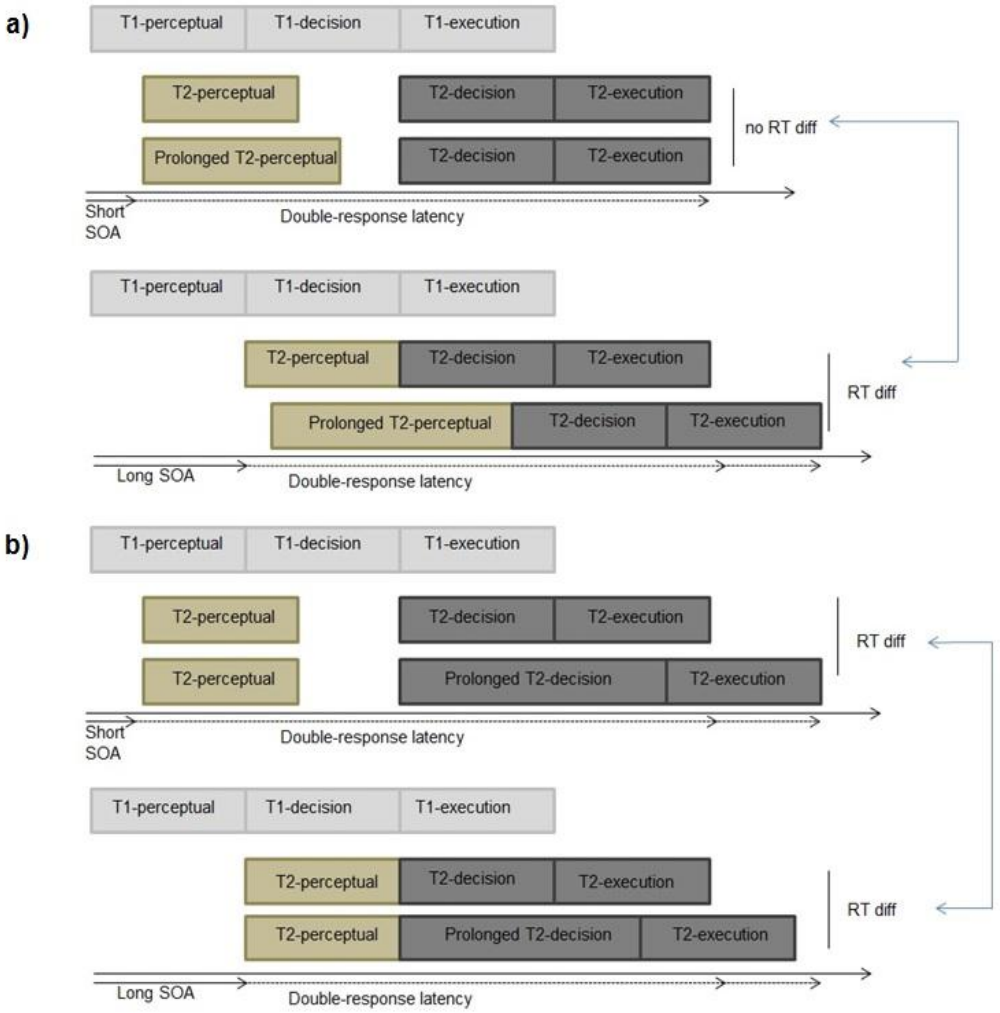

Figure 1.10. The stages proposed to underlie motor responding. The image illustrates how elongation of either the **(a)** perceptual or **(b)** decision stages can influence RT in task 2 (T2). When two tasks are completed sequentially, the decision stage of the first task (T1) creates a bottleneck that must be completed before the decision stage for T2 can begin. **(a)** illustrates that at short SOAs, the extension of the perceptual phase of T2 can be absorbed into the bottleneck, and causes no effect on RT to T2. At longer SOAs, the perceptual stage enters the post-bottleneck phase and delays the onset of the decision stage to T2, thereby increasing the corresponding RT. **(b)** illustrates that as the decision stage for T2 occurs post-bottleneck, there are no difference in RTs to T2 when SOA is short vs. long. Image adapted from Verbruggen *et al.* (2010).

However, it must be noted that these findings may be due to the influence of TMS at locations distal to the site of application (Siebner *et al.*, 2010). Specifically,

[11] Improvement in the execution of action sequences was found subsequent to intermittent theta burst stimulation- a variant of TMS known to increase cortical excitability (Huang *et al.*, 2005, 2011).

TMS to the ventral rIFG has the potential to influence neuronal excitability in the posterior ventral premotor cortex (Aron, Robbins, & Poldrack, 2014b), an area known to have a strong TMS-induced inhibitory influence over the motor cortex when action plans require reprogramming (Buch *et al.*, 2010). Furthermore, Verbruggen *et al.* (2010) observed a speeding of goRT as well as impaired updating latencies after TMS to the rIFG (Figure 1.9). This could be indicative of the rIFG's involvement in the setting and adjustment of response thresholds (although note, there was no change in goRT or accuracy identified by Chambers *et al.*, *2*006 who also found prolonged SSRT after TMS to the rIFG). Indeed, in a recent meta-analysis, Levy & Wagner (2011) proposed a functional dissociation between the posterior and anterior rIFG (the *pars opercularis* and the *pars triangularis*, respectively), with the former theorised to support the updating of action plans and the latter theorised to support response selection under ambiguous conditions.

Regardless of the interpretation, these TMS studies indicate that the rIFG is not solely responsible for the implementation of inhibition and can support action updating processes more broadly. Consistent with this, overlapping activity in the *pars opercularis* has been observed under no-go and DT conditions (i.e. when stimulus and signals are presented simultaneously; Dodds, Morein-Zamir, & Robbins, 2011). Importantly, activity was stronger under DT relative to no-go conditions, which the authors argue is the result of increased response control demands associated with executing two simultaneous responses as opposed to inhibiting a single response.

The work reviewed up until this point largely formed the basis of the studies presented in this thesis, and motivated my interest in controlling for non-inhibitory processes in response inhibition research. There has since been a rise in interest in this area and a number of papers have been published demonstrating increasing awareness of controlling for confounding processes. The rIFG has remained the focus of these studies, although none support a specific inhibitory module within this region.

Like Verbruggen *et al.* (2010), Chatham *et al.* (2012; see also review from Banich & Depue, 2015) employed a DT alongside a SST (i.e. with a delay between stimulus and signal onsets), but with an aim of establishing the role of the rIFC in context monitoring and inhibitory control[12]. In a series of experiments, Chatham *et al.*

[12] Here, the DT required the go response to be repeated as opposed to the initiation and execution of a new motor plan as employed by Verbruggen *et al.* (2010).

(2012) concluded that the rIFC is recruited in response to monitoring demands when actions require adjustment, even without any explicit inhibitory requirements. Using functional magnetic resonance imaging (fMRI) they identified substantial overlap in activity across the rIFC under both SST and DT conditions (Figure 1.11a), as well as greater activity across all rIFC sub-regions when double signals, relative to stop signals, were presented (Figure 1.11c). This was argued to reflect increased mental effort in the DT relative to the SST, and was supported by increased pupil diameter under conditions of context monitoring (monitoring for behaviourally relevant stimuli) relative to response inhibition. Pupil diameter was increased during go trials in the SST and DT relative to during stop signals, and increased upon presentation of signal trials in the DT relative to those presented in the SST. Chatham *et al.* (2012) also report that event related potentials (ERPs), as measured by EEG, were greater in the DT relative to the SST, particularly in components classically associated with the response inhibition (the so-called Stop P3, or No/Go P3)[13].

Chatham *et al.*'s (2012) findings refute the possibility that the rIFG houses a specialised node for implementing response inhibition. However, Aron *et al.* (2014a, 2014b) argue that greater recruitment of the rIFG under DT relative to SST conditions is confounded by order effects as Chatham *et al.* (2012) always provided participants with the DT before the SST. Furthermore, they propose that the presentation of salient signals always partially engages the inhibition system (i.e. a partial 'brake') - evidenced by the slowing of RTs to signal, relative to go, trials in the DT. However, as mentioned above, this slowing could be the result of capacity sharing (Miller *et al.*, 2009; Navon & Miller, 2002; Tombu & Jolicœur, 2002, 2003, 2005) and recent work has highlighted that the presentation of infrequent stimuli is likely to recruit attentional, as opposed to inhibitory, mechanisms (Leiva *et al., 2*015). Furthermore, slowing of RTs in the presence of salient stimuli is not always found. For example, in a recent study, Erika-Florence *et al.* (2014; see also Hampshire, 2015) found no evidence of slowing when participants were presented with infrequent signals but were not required to adjust their responses. rIFG activity was also observed when participants performed this task, providing further support for the target detection account of rIFG function.

[13] Chatham *et al.* (2012) report the N2 (an earlier ERP often discussed in relation to the Stop P3) was not of interest but was observed to be increased in the SST relative to the DT. They argue this to be representative of increased response conflict as opposed to inhibition per se.

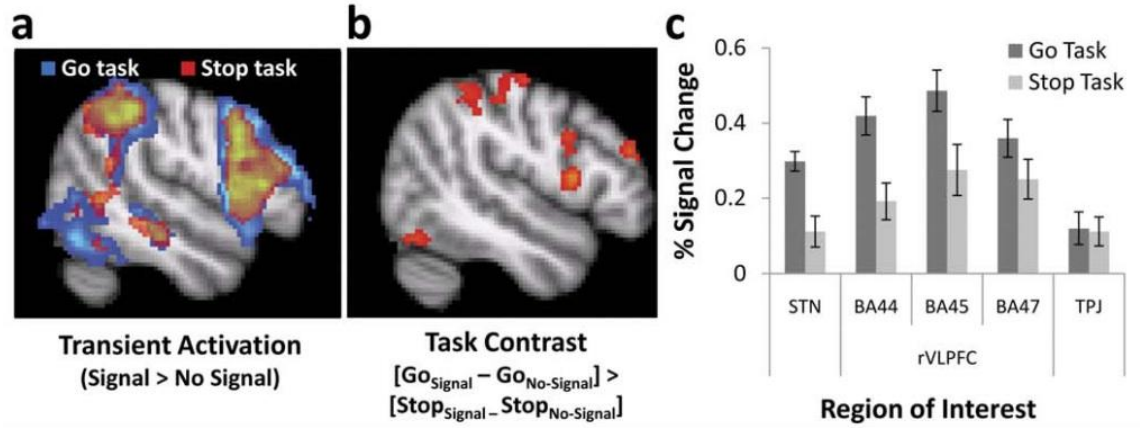

Figure 1.11. Image from Chatham *et al.* (2012) demonstrating **(a)** the overlap within the rIFC under double-response (go) and response inhibition (stop) conditions; **(b)** the presence of greater recruitment of posterior rIFG and rIFJ activity associated with go signal trials relative to go no-signal trials and all trials in the SST; **(c)** the increased %BOLD activity associated with the go task relative to the stop task in the subthalamic nucleus (STN), *pars opercularis* (BA44), *pars triangularis* (BA45), *pars orbitalis* (BA47) and the temporoparietal junction (TPJ).

Erika-Florence *et al.* (2014) employed 4 separate tasks (monitor, inhibit, respond and complex, Figure 1.12) to establish the role of the rIFG in response inhibition and the acquisition of novel, rule-based instructions. Independent components analysis of fMRI data (a data-driven method of extracting statistically independent maps based on the time course of activity within voxels), revealed 7 separate regions of interest (ROIs) within the rIFC/insula. Activity within ROIs was averaged separately for each task. Contrasting the activity associated with the requirement to *inhibit* a response against all other tasks revealed no significant regions of activity. No difference in rIFG recruitment was found when successful *inhibit* trials were contrasted against unsuccessful *inhibit* trials (consistent with other studies; e.g. Boehler *et al., 2*010). Although Erika-Florence *et al.* (2014) argue this supports the conclusion that the rIFC is not recruited to implement response inhibition, unsuccessful stops still likely engage the stopping process (Aron *et al.*, 2014a, 2014b; Swann, Tandom, Canolty *et al.*, 2009; Swann, Poizer, Houser *et al.*, 2011). As activity in the rIFC was greater in early vs. late *inhibit* task blocks, Erika-Florence *et al.* (2014) conclude the rIFC acts to detect infrequent stimuli and to acquire novel rules. This claim is supported by a recent review (Domenech & Koechlin, 2015).

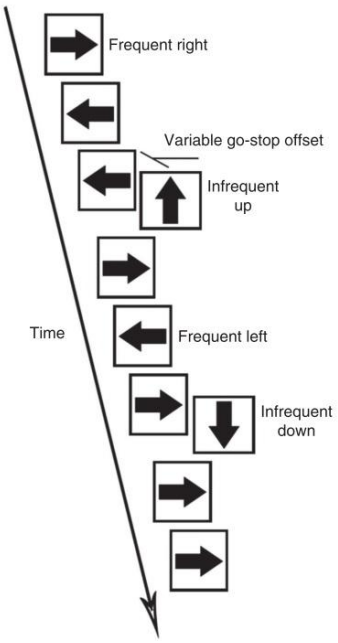

Figure 1.12. The different stimuli presented by Erika-Florence *et al.* (2014). In the *monitor* and *inhibit* tasks participants were to respond to the direction of the frequent left and right pointing arrows. On 26% of trials, infrequent up or down facing arrows were presented. In the *monitor* task these were to be ignored and in the *inhibit* task, participants were instructed to try and withhold their response. In the *respond* and *monitor* tasks, participants were instructed to execute responses only to the infrequent up and down facing arrows. In the *respond* task a single response was made to each trial type, whereas in the *complex* task single responses were executed upon presentation of upward facing arrows and a concurrent double-response upon presentation of downward facing arrows.

Aron *et al.* (2014b) argue that a specialised rIFG inhibitory module went undetected in the study by Erika-Florence *et al.* (2014) because their *respond* and *complex* tasks (Figure 1.12) likely involved the withholding, and thus inhibition, of a prepared action plan. However, all trials would require restraint and thus this interpretation does not account for differences between frequent and infrequent trials. Furthermore, this argument contradicts Aron *et al*.'s own claim that a specialised rIFG inhibitory node acts to support reactive inhibition of a prepotent response as opposed to proactive action restraint[14]. Aron *et al.* (2014b) also argue that the ROIs interrogated by Erika-Florence *et al.* (2014) did not include the specific region of the rIFG that implements response inhibition. However, re-analysis of the data with the precise co-ordinates of the supposed inhibition node (as provided by Aron *et al.*, 2014b -

[14] This claim was made in reference to Stuss & Alexander's (2007) cognitive control framework and their omission of inhibition as a core executive function. Aron *et al.* (2014a) argue that Stuss & Alexander (2007) rely on evidence from Stroop and go/no-go tasks do not have the "requisite prepotency to engage the form of response inhibition we have postulated" (p179).

MNI=48,16,18 - also reported in Levy & Wagner, 2011), revealed no functional specificity associated with response inhibition (Hampshire, 2015). In addition, this region was found to be commonly recruited across a range of tasks (Hampshire, 2015; see also Hampshire *et al.*, 2010; Erika-Florence *et al.*, 2014)[15]. Finally, Hampshire (2015) argues that the pattern of activity demonstrated across the rIFC may represent sub-regions that support different aspects of the motor plan, including the detection, internal processing and execution of a response. An interpretation similar to Verbruggen *et al.*'s (2014a) conceptual framework mentioned above. The numerous roles that the rIFC appears to play under different response control conditions has led Hampshire *et al.* (Hampshire, 2015; Hampshire & Sharp, 2015a, 2015b) to propose that the rIFG is recruited flexibly depending on task demands. The proposed role of rIFG as part of a multiple-demand cortex is discussed next.

1.2.1.3. The rIFG as part of a multiple demand cortex

Hampshire & Sharp (2015a) have argued that the potential for a rIFG-specific role in response inhibition is computationally inefficient and unsubstantiated. Instead they propose that response inhibition is just one of many different intentional processes that are implemented by a multiple demand cortex (MDC). The MDC is conceptualised as a flexible, domain-general system that acts to support numerous cognitive processes (Duncan, 2000, 2001, 2010, 2013; Duncan & Owen, 2000; Fedorenko *et al.*, 2013). This ability is assumed to be the result of the division of complex processes into smaller and more manageable sub-components (Duncan, 2001, 2010, 2013). The MDC was proposed in response to the common recruitment of brain regions by different cognitive processes (e.g. see Duncan & Owen, 2000), and the observation that everyday behaviours and actions do not arise as a set of isolated processes, but rather are the product of a series of sub-tasks (Duncan, 2010, 2013). Duncan posits that activity throughout fronto-parietal regions are at the core of the MDC (Figure 1.13) and that

[15] Hampshire (2015) ran an additional fMRI study employing variants of the go/no-go task. A *monitor* task that required participants to only monitor the stimuli and to make no motor responses to either targets or distracters. A *count* task that required participants to count the number of targets, without responding to either targets or distracters. A *prepare* task where participants were to respond only on the last trial in a block if it was a target (incidentally block sequences varied in length which meant participants always responded to targets). A *respond images* and a *respond words* task where participants were instructed to respond only to target images/words. An *inhibit* task where participants were to respond to all stimuli apart from the target.

subtle adjustment to neuronal firing patterns can make a vast difference to the cognitive processes that are ultimately realised.

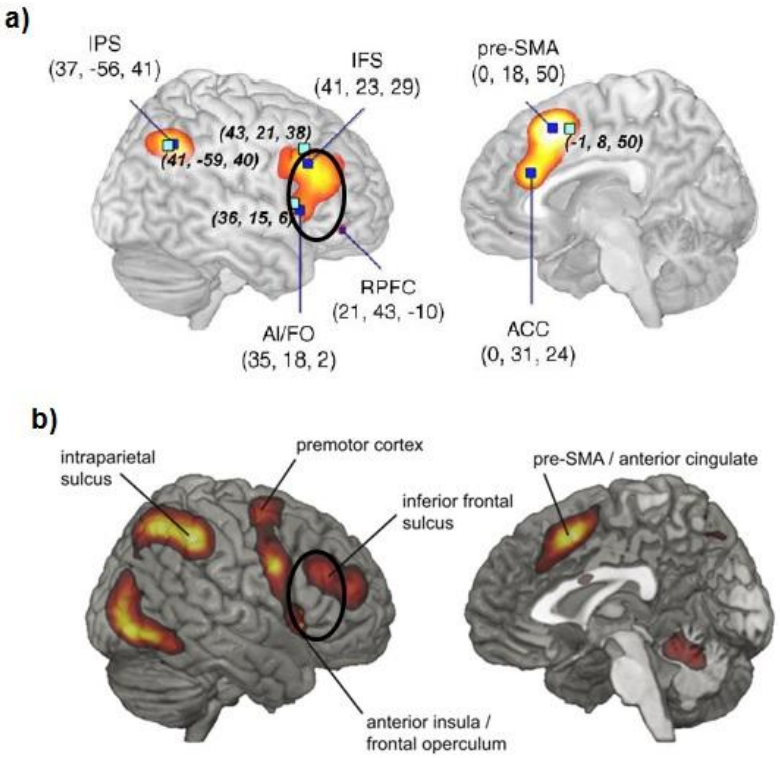

Figure 1.13. The multiple demand cortex (MDC) as conceived by Duncan. The images demonstrate the reduction in size of the MDC from its original conception **(a)** until recently **(b)**. Of particular note is the exclusion of the IFG in more recent models (region within the black ovals). Aron *et al.* (2015) argue that this demonstrates that response inhibition cannot be part of the MDC. Images adapted from Duncan (2010) and Duncan (2013).

Hampshire & Sharp (2015a) propose that the MDC may operate via a combination of top-down potentiation and lateral inhibition. Top-down potentiation biases activity in neurons that code for specific representations to be favoured when competing with others in lateral inhibition (that is, the ability for neighbouring neurons to reduce the excitability of one another; Aron, 2007). In the context of the SST, Hampshire & Sharp (2015a) postulate that the expectation of a stop signal primes neurons involved in motor responding by down-regulation. The detection of a stop signal increases the excitability of down-regulated neurons. However, increased strength of relevant representations slows responding due to the requisite lateral

inhibition. This slowing can be observed in the elongation of RTs and the ultimate cancellation of an action.

The MDC offers a parsimonious account of the range of cognitive processes the rIFG appears to support. However, Aron, Cai, Badre, & Robbins (2015) refute that response inhibition is merely the product of MDC adjustments and that recent representations of the MDC no longer include the IFG (Figure 1.13b; Duncan, 2013). Furthermore, they argue that Hampshire *et al.*'s (Erika-Florence *et al.,* 2014; Hampshire *et al.,* 2010; Hampshire, 2015) position is based on methodological imprecision, including the lack of task randomisation, and poor SST performance (although see rebuttal by Hampshire & Sharp, 2015b). Thus further work, accounting for such limitations, is required.

1.2.2. The pre-supplementary motor area

The pre-SMA (medial Brodmann's area 6) lies in the medial wall of the superior frontal gyrus, anterior to the primary motor cortex and superior to the anterior cingulate cortex (ACC) (Figure 1.14). Together, the pre-SMA and ACC form the medial frontal cortex, which are typically discussed in relation to the adjacent DLPFC, due to the shared anatomical and functional connectivity (e.g. Roth, Johnson, Tokoglu *et al.,* 2014). The pre-SMA, like the rIFG, has been implicated in inhibitory control and an array of other cognitive processes. Here, I discuss the role of the pre-SMA in response inhibition with respect to proactive and reactive control and its proposed roles in performance monitoring and conflict resolution.

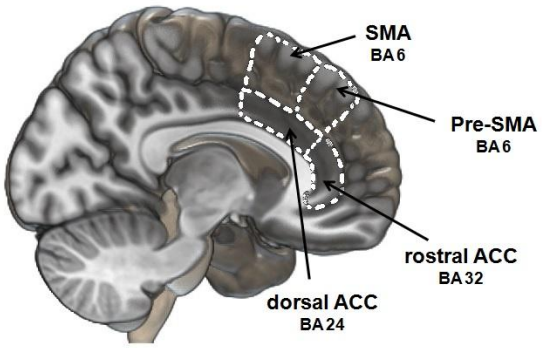

Figure 1.14. The location of the pre-SMA, SMA and anterior cingulate cortex (divided into dorsal and rostral regions). Corresponding Brodmann's areas (BA) shown.

1.2.2.1. The pre-SMA, reactive and proactive inhibition

For advocates of a specialised inhibitory node that does not reside in the lateral prefrontal cortex, the pre-SMA is argued to be a plausible source (e.g. Duann, Ide, Luo, & Li, 2009; Hampshire *et al.*, 2010; Li *et al.*, 2006; Sharp *et al.*, 2010; Tabu, Mima, Aso, Takahashi, & Fukuyama, 2011). There is considerable evidence to support the role of the pre-SMA in response inhibition (see Section 1.2). However, there is much debate as to whether the pre-SMA acts to support reactive inhibitory control, proactive inhibitory control, or both (e.g. Aron *et al.*, 2007; Li *et al.*, 2006). As noted above, reactive inhibition refers to the global cancellation of all actions in response to exogenous (and theoretically internal) stimuli (De Jong *et al.*, 1990, 1995; Frank, 2006; Wiecki & Frank, 2011; Verbruggen & Logan, 2009b; Aron & Verbruggen, 2008; Aron, 2011). Conversely, proactive inhibition is theorised to be a slower, more selective form of response inhibition (when participants are told they have to inhibit a specific response), which is presumed to be recruited under conditions where there is sufficient time to plan the cancellation of an action (Aron & Verbruggen, 2008; Aron, 2011).

Evidence that the pre-SMA acts to support proactive control is largely based on observed elevations in neuronal activity prior to response execution and response inhibition. In monkeys, single cell recordings have found increased neural activity during action preparation and responding (e.g. Hoshi & Tanji, 2004; Scangos, Aronberg, & Stuphorn, 2013). In humans, sustained pre-SMA activity is found in imaging studies exploring task preparation (Brass & von Cramon, 2002; Hester, Murphy, Foxe *et al.*, 2004) and increased neural activity (as measured by electrocorticography and electromyography) has been found during response preparation and prior to successful stopping in the SST (Ikeda, Lüders, Burgess &

Shibasaki, *et al.,* 1992; Swann, Cai, Conner *et al.,* 2012). In TMS studies, the disruption of proactive inhibition in a SST has been found to correlate with pre-SMA activity (Majid, Cai, Corey-Bloom, & Aron, 2013) and the ability of the rIFG to suppress motor output has been found to be dependent on the pre-SMA (Neubert & Klein, 2010). Furthermore, pre-SMA activity is increased in task blocks where stop signals are possible - i.e. conditions where proactive response strategies are likely adopted (Chikazoe *et al.,* 2009; Vink, Kaldewaij, Zandbelt *et al.,* 2015). Greater pre-SMA activity is also found in participants who demonstrate greater efficiency of inhibitory control (i.e. by shorter SSRTs; Chao, Luo, Chang, & Li, 2009; Li *et al.,* 2006; Mostofsky, Schafer, Abrams *et al.,* 2003).

Pre-SMA activity is elevated in response to cues that emphasise speed over accuracy, and has been argued to reflect the lowering of response thresholds (Forstmann, Dutilh, Brown *et al.,* 2008; Mansfield, Karayanidis, Jamadar *et al.,* 2011; although note that Ivanoff, Branning, & Marois, 2008, have suggested that speed-accuracy tradeoffs modulate activity in lateral prefrontal cortex). Increased activity associated with shorter SSRT (Chao *et al., 2*009; Li *et al., 2*006; Mostofsky *et al., 2*003) may demonstrate enhanced capability to set and adjust response thresholds, successfully balancing speed-accuracy tradeoffs (although adjustments in response thresholds do not necessarily influence SSRT; Verbruggen & Logan, 2009c, final experiment). Recruitment of the pre-SMA is increased under conditions of volitional movement relative to actions triggered by exogenous signals (Nachev, Rees, Parton, & Kennard, 2005), which presumably permits greater control over corresponding response thresholds (Forstmann, Brass, Koch, & Von Cramon, 2005). Consistent with this possibilty, pre-SMA activity appears dependent on task-familiarity, reward and motivation (Scangos *et al.,* 2013; see also review Aron, 2011) and is particularly elevated under novel task conditions (Chen *et al.,* 2009) – i.e. activity within the pre-SMA is modulated in situations within which individual's are likely to actively set and adjust response thresholds as means to achieve goal-directed behaviour.

Response preparation is also dependent on the ability to maintain rules within working memory, argued to be reliant on the DLPFC (Crone, Wendelken, Donohue *et al.,* 2006; Mostofsky et al., 2003; Simmonds, Pekar, & Mostofsky, 2008; see D'Esposito, Postle, & Rypma, 2000, for a review). Strong interconnectivity between the DLPFC and pre-SMA (e.g. Roth *et al.,* 2014) provide potential for interactions during response preparation. Increasing working memory load in go/no-go tasks increases

activity in the DLPFC (Mostofsky *et al.,* 2003; Barber *et al., 2*013; see also meta-analysis by Criaud & Boulinguez, 2013) and in the pre-SMA (Barber *et al.,* 2013). Although it might be expected that pre-SMA activity would decrease with increasing load due to inefficiency in setting response thresholds, such increases may be associated with the number of response options available (Mostofsky *et al.,* 2003). Furthermore, the ability for the pre-SMA to create task sets (Forstmann *et al.,* 2005; Mars *et al., 2*007), likely operates via the DLPFC to update working memory representations (Brass *et al.,* 2005; Bunge, Kahn, Wallis *et al.,* 2003; Crone *et al.,* 2006).

On the other hand, there is much evidence to suggest that the pre-SMA supports reactive inhibition. In monkeys, pre-SMA neurons are active upon presentation of stop signals, and this activity is delayed on unsuccessful no-go trials (indicating the late engagement of the stop process; Isoda & Hikosaka, 2007). In humans, EEG activity within the vicinity of the pre-SMA is heightened prior to successful stopping (Swann *et al.,* 2012). Furthermore, TMS has been found to impair SSRT, but not response tendencies (Cai *et al., 2*012). More recently evidence has indicated that the pre-SMA may act to implement response inhibition directly, triggered by projections from the rIFC (Duann *et al.,* 2009; Rae, Hughes, Anderson, & Rowe, 2015; Zandbelt *et al., 2*013). However, activity in the pre-SMA is also enhanced when responses are required in the absence of preparation and when decisions need to be made within stringent time frames (Forstmann *et al.,* 2008). Thus, given the evidence discussed above regarding the pre-SMA's role in setting response thresholds, it is possible that its reactive engagement is associated with processes aside from direct implementation of inhibition. The potential for the pre-SMA to support performance monitoring and conflict detection and resolution processes is discussed in Section 1.2.2.2.

Finally, it is possible that the pre-SMA acts to support both proactive and reactive control. Impairments in both have been found subsequent to TMS applied to the pre-SMA (Obeso *et al.,* 2013) and van Belle *et al.* (2014) have recently found overlapping activity in this region during both proactive and reactive inhibition (using independent components analysis). Such potential is in-keeping with the proposal that the pre-SMA is a 'flexible hub' that can be recruited differentially depending on task demands (Criaud & Boulinguez, 2013). Thus the potential for this region to support processes other than response inhibition must be considered.

1.2.2.2. The pre-SMA, performance monitoring and conflict resolution

SST performance is dependent on participants' ability to mediate between speed and accuracy of responding. Efficient implementation of both proactive and reactive response strategies are likely reliant on a system capable of rapid performance evaluation to make such adjustments. The medial prefrontal cortex has been proposed to support a range of related processes (e.g. Botvinick *et al.*, 2001; Nachev *et al.*, 2007; Klein, Endrass, Kathmann *et al.*, 2007; Taylor, Nobre, & Rushworth, 2007).

Successful performance monitoring relies on the evaluation of anticipated response-outcome associations for which error detection is crucial. In monkeys, single cell recordings of pre-SMA and SMA neurons have established unique populations that react differentially to reward expectancy, the actual reward and incompatibility between them (Scangos *et al.*, 2013). In healthy participants, imaging studies have found increased pre-SMA activity in response to errors (e.g. Garavan, Ross, Murphy *et al.*, 2002) and when outcomes are not in-line with expectations (Mars *et al.*, 2008; Zanolie, Van Leijenhorst, Rombouts, & Crone, 2008).

While the above evidence is indicative of a role in error monitoring and detection, Juan & Muggleton (2012) refute this possibility. They argue that if the pre-SMA was crucial for error-related processing, disruption by TMS would increase commission errors and reduce RTs (due to the reduction of post-error response slowing). However, although commission errors are increased, goRTs are typically elongated (e.g. Obeso *et al.*, 2013). This might be demonstrative of a less efficient ability to adjust response strategies after unsuccessful stop signal trials, for which the pre-SMA (along with the IFG and subthalamic nucleus), has been hypothesised to support (Danielmeier, Eichele, Forstmann *et al.*, 2011; Danielmeier & Ullsperger, 2011; King, Korb, von Cramon, & Ullsperger, 2010). Furthermore, TMS pulses are typically given soon after the presentation of a task cue or go stimulus/signal and thus disruption of post-error activity is unlikely (Juan & Muggleton, 2012).

A more likely candidate for error-related processing is the ACC. The ACC is consistently recruited in imaging studies employing executive control tasks (e.g. Brown & Braver, 2005; MacDonald, Cohen, Stenger & Carter, 2000; Sharp et al., 2010), and errors typically indicate the need for top-down control (Miller & Cohen, 2001). Increased activity within the ACC has been found after inhibition failure (e.g. Chevrier *et al.*, 2007), and has been implicated as the source of error-related negativity in studies

using EEG (e.g. Dimoska, Johnstone, & Barry, 2006; Jodo & Kayama, 1992; Menon, Adleman, White *et al.,* 2001; Senderecka, Grabowska, Szewczyk *et al.,* 2012; see Ridderinkhof et al., 2004; Veen & Carter, 2002; Yeung & Nieuwenhuis, 2009, for reviews). Where error likelihood is matched, both pre-SMA and ACC show increased activity in participants with short relative to long SSRTs (Li *et al.,* 2006). This could either indicate the ACC and pre-SMA are not involved in error detection or that they support additional processes required to ensure successful SST performance. In particular, time constraints have also been found to influence pre-SMA and ACC activity (Forstmann *et al.,* 2008; Garavan, Ross, Kaufman, & Stein, 2003) and may be due to adjustment of response thresholds to successfully arbitrate between speed and accuracy.

The co-activation of the pre-SMA and ACC may be due to the recruitment of simultaneously occurring processes. Specifically, error rates increase with increasing response options and are likely associated with response conflict (the result of competing representations; Botvinick *et al., 2*001). Functional dissociation of the ACC and pre-SMA have been demonstrated, with the former associated with error likelihood and anticipation and the latter associated with conflict detection (e.g. Garavan *et al., 2*003; Rushworth, Walton, Kennerley, & Bannerman, 2004; Ullsperger & von Cramon, 2001; Yeung & Nieuwenhuis, 2009). Indeed, pre-SMA (Nachev *et al.,* 2007; Garavan *et al.,* 2002; Forstmann *et al.,* 2008; Mars *et al., 2*009; see also Aron *et al., 2*007; Yamamoto, Kushima, Kimura *et al.,* 2015), but not ACC activity (Emeric, Brown, Leslie *et al.,* 2008; Ito, Stuphorn, Brown, & Schall, 2003; Nakamura, Roesch, & Olson, 2005) is elevated upon detection of response conflict.

The pre-SMA has been found to resolve, as well as detect, response conflict. Taylor *et al.* (2007) investigated the effects of TMS to the pre-SMA on the lateralised readiness potential (LRP) while participants completed an Eriksen Flanker task. In this task, participants are instructed to respond to a central stimulus as fast and accurately as possible when flanked by either congruent or incongruent stimuli (Figure 1.15a). Incongruent flankers elicit conflict due to the presentation of competing representations. When no flankers or congruent flankers are presented, a negative ERP is observed in the motor region contralateral to the hand responded with. However, a positive ERP is observed under conditions of task conflict (Figure 1.15b). Taylor *et al.* (2007) found the application of TMS influenced LRPs on incongruent trials only. Thus TMS disrupted

the ability for conflict between competing representations to be resolved as opposed to simply detecting their presence.

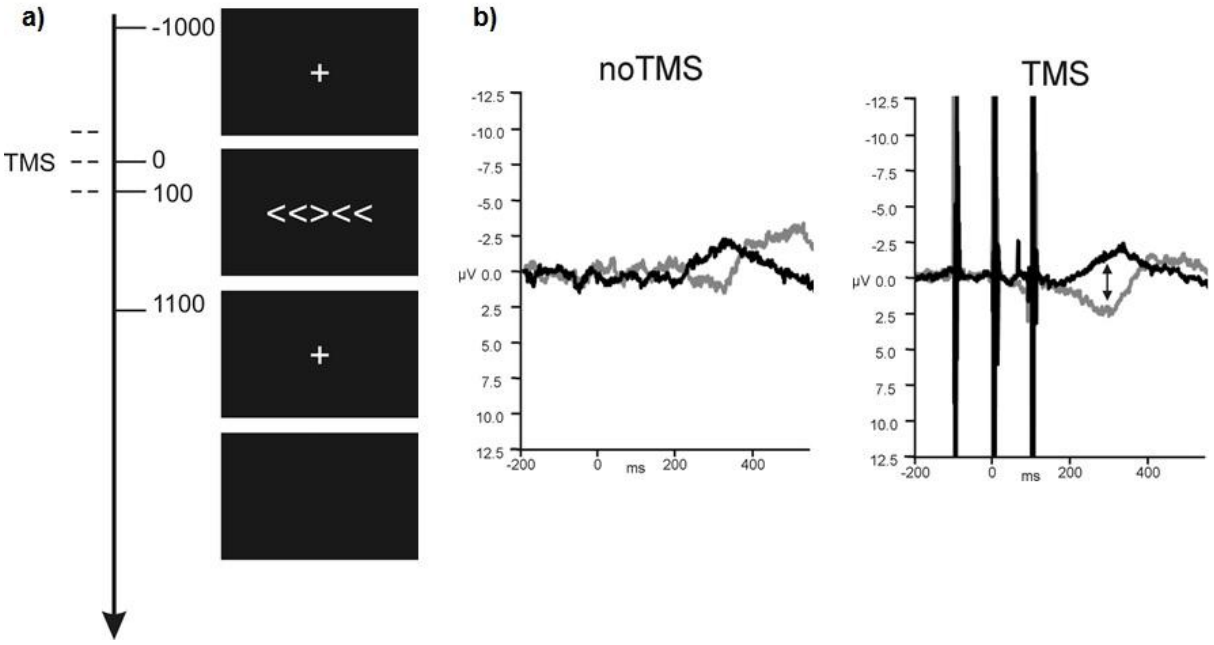

Figure 1.15. Summary of the task and findings from Taylor *et al.* (2007). **(a)** The Eriksen-Flanker task employed. Participants were instructed to respond to the direction of the central arrow as fast as possible. The central arrow was either flanked by congruent stimuli or incongruent stimuli. That is, arrows facing the same or opposing directions, respectively. **(b)** The effect of TMS on LRPs when applied to the pre-SMA (the plots report negative LRPs upwards). The black trace represents the LRP on congruent trials and the grey trace represents the LRP on incongruent trials. On no TMS trials the LRP corresponding to incongruent trials is offset relative to the congruent LRP (see effects from approximately 300ms onwards) suggestive of preparation of the incorrect response. On TMS trials, there was a significant difference in congruent and incongruent LRPs (illustrated by the black arrows) owing to the TMS-induced positive LRP on incongruent trials.

It has also been argued been that response inhibition and response selection represent manifestations of the same process, that differ only semantically (Hampshire & Sharp, 2015a, 2015b; Mostofsky & Simmonds 2008; see also Verbruggen et al., 2014a). Indeed, many studies implicate the pre-SMA in supporting response selection (Sakai et al., 2000; see Mostofsky & Simmonds, 2008, for a discussion), which is the necessary outcome of conflict resolution. Increased response options could explain why the pre-SMA is sometimes elevated under conditions of increased working memory load (e.g. Barber *et al.*, 2013; see also meta-analysis Criaud & Boulinguez, 2013).

It is clear that the pre-SMA supports multiple processes that are required for successful SST performance, which appear to be both proactive and reactive. It is possible that this region may support and implement response inhibition by a combination of these non-inhibitory processes. The pre-SMA may be engaged proactively in the preparation of a stop signal and the creation of task sets, but reactively by the detection and resolution of response conflict. It is also likely that some processes are engaged both proactively and reactively, such as the generation and adjustment of response thresholds.

1.2.3. Subcortical contributions

Subcortical activity is at the heart of motor control (Middleton & Strick, 2000; Mink, 1996; Utter & Basso, 2008). Known to receive projections from the cortex, the BG are hypothesised to assimilate and direct signals to the thalamus (THAL) to ultimately facilitate or suppress motor output (Figure 1.16, Albin, Young, & Penney, 1989; Alexander & Crutcher, 1990, Nambu, Tokuno, & Takada, 2002). In the SST, lesions to BG nuclei have been found to prolong SSRT (Eagle & Robbins, 2003; Rieger, Gauggel, & Burmeister, 2003) and immaturity of fronto-BG regions are often held accountable for the poor performance on tasks involving inhibitory control in children relative to adults (Durston *et al.*, 2003; Rubia, Smith, Wooley *et al.*, 2006). The degeneration of BG structures and abnormal structural and functional connectivity between cortical-subcortical regions have been implicated as the source of inhibitory control deficits in many neurological and psychiatric diseases (e.g. Alexi, Borlongan, Faull *et al.*, 2000; Dirnberger, Frith, & Jahanshahi, 2005; Hirjak, Wolf, Wilder-Smith *et al.*, 2015; see Utter & Basso, 2008, for a review).

Three distinct cortico-subcortical pathways are hypothesised to be involved in the implementation of response execution as well as proactive and reactive response inhibition: the direct, indirect and hyperdirect pathways, respectively (Albin *et al.*, 1989; Alexander & Crutcher, 1990; Nambu *et al.*, 2002; Aron and Poldrack, 2006; Aron, 2011). Under this model, it is proposed that subcortical gating mechanisms exist to facilitate or suppress actions via projections received from the frontal cortex (see also Wiecki & Frank, 2011; Schroll & Hamker, 2013). To make a response a fronto-striatal-pallidal (direct) pathway is activated, which can be blocked when inhibition is required via the indirect or hyperdirect pathway. It has been proposed that the subthalamic

nucleus (STN) is crucial to the implementation of inhibition and acts to suppress THAL activation via inhibitory projections (Nambu *et al.,* 2002; Aron & Poldrack, 2006; Aron, 2011). How this is achieved, however, differs between the indirect and hyperdirect pathways.

Aron and Verbruggen (2008) argue that a selective mechanism is recruited when an individual has sufficient time to plan the suppression of motor activity (i.e. proactive inhibition). Such inhibition is theorised to be implemented via the indirect pathway, which comprises a fronto-striatal-pallidal-subthalamic circuit (Figure 1.16; Nambu *et al.,* 2002; Aron and Poldrack, 2006; Aron, 2011). Alternatively, if an external stimulus to inhibit a response occurs unexpectedly then a global mechanism may be recruited to drive inhibition. Such reactive inhibition (Aron and Verbruggen, 2008) is argued to be implemented by a fast, hyperdirect route involving fronto-subthalamic systems (Aron, 2011). The key difference between these pathways is that under conditions where reactive inhibition is required, the striatum (STR) and globus pallidus externa (GPe) are bypassed to implement inhibition quickly (i.e. the hyperdirect pathway), whereas when individuals have time to prepare the stop response, implementation of inhibition involves recruitment of the STR and GPe (i.e. the indirect pathway; Aron, 2011).

With respect to response inhibition as required in the SST, it is unclear whether the indirect or hyperdirect route takes precedence, given the proposed recruitment of both proactive and reactive processes discussed above. Furthermore, the temporal duration between recruitment of hyperdirect and indirect activity appears to be very short (approximately 22ms; Nambu *et al.,* 2002[16]) and thus recruited pathways could be readily switched. As such, research has tended to focus on the roles of the major input nuclei hypothesised to implement response inhibition- the STR and STN.

[16] This latency is based on microstimulation of the primary motor cortex in macaques. Activity in the GPi is found to undergo 3 separate phases of excitability. An initial excitation phase occurs approximately 8ms after stimulation and is hypothesised to reflect activity in the hyperdirect pathway. This is followed by an inhibition phase at approximately 21ms after stimulation and is hypothesised to reflect activity in the direct pathway. Finally, another wave of excitation occurs approximately 30ms post-stimulation and is thought to represent activity in the indirect pathway.

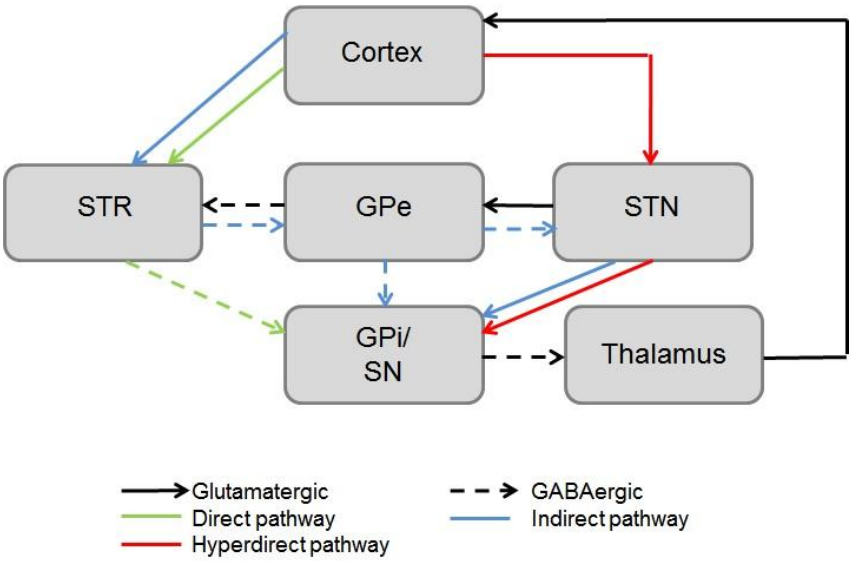

Figure 1.16. The hypothesised model of cortico-subcortical pathways involved in implementing inhibition via the basal ganglia. The green arrows represent the direct pathway, the blue arrows represent the indirect pathways and the red arrows represent the hyperdirect pathway. Black arrows represent no specific pathways. GABAergic projections are denoted by the dashed lines, and Glutamatergic by the solid lines. The ***direct*** pathway enables responses to be executed and is thought to be triggered via excitatory projections from the frontal cortex being received by the striatum (STR), which in turn sends inhibitory projections to the globus pallidus interna (GPi) and substantia nigra pars reticulate (SN). The indirect and hyperdirect pathways are proposed to block the actions of the direct pathway via the STN. The ***indirect*** pathway involves inhibitory projections being sent from the STR to the globus pallidus externa (GPe); inhibitory projection to the STN is then reduced, increasing excitation to the GPi and SN, which in turn inhibits activity in the thalamus. The ***hyperdirect*** pathway is a faster mechanism in which direct frontal input is received by the STN (bypassing the STR), which sends excitatory output to the GPi/SNr, and which in turn inhibits the thalamus. Figure adapted from Schroll & Hamker (2013).

1.2.3.1. The striatum

The STR is proposed to house neurons that respond differently when recruited under the direct and indirect pathways. GABAergic medium spiny neurons (MSNs) are proposed to have differential effects depending on the nuclei they project to (Figure 1.16). The importance of the STR in response inhibition is evidenced in rat studies where lesions increase SSRT by up to 60% (Eagle & Robbins, 2003). In imaging studies, STR activity is elevated upon successful inhibition of a stop signal (Zandbelt & Vink, 2010), and is met with a corresponding decrease in primary motor cortex activity (Zandbelt & Vink, 2010).

As the input region for the indirect pathway, the STR is proposed to support proactive control and there is much evidence to support this. For example, STR activity is increased upon presentation of a cue to stop (Vink *et al.*, 2015) rather than a go stimulus (Zandbelt, Bloemendaal, Hoogendam *et al.*, 2013) and has been found to increase with stop signal probability (Zandbelt & Vink, 2010; see also (Jahfari, Verbruggen, Frank *et al.*, 2012) and reward anticipation (Harsay, Cohen, Oosterhof *et al.*, 2011). Longer goRTs have been found to be associated with increased STR activity (Vink, Kahn, Raemakers *et al.*, 2005, although not found by Zandbelt & Vink, 2010) and similar firing rates of STR neurons in rats have been found when both slow responses are executed and when stop signals are successfully inhibited (Schmidt, Leventhal, Mallet *et al.*, 2013). Although the original pathways models (Albin *et al.*, 1989; Alexander & Crutcher, 1990) suggest the presence of functionally specific neurons involved in response execution and response inhibition, Calabresi *et al.* (2014) propose that STR neurons can be recruited for either pathway depending on response requirements (and can be recruited simultaneously as opposed to sequentially as argued by Nambu *et al.*, 2002). Consistent with this proposition, studies of mice MSNs *in vivo* have established no difference in the pattern of projections received from cortical structures (Huerta-Ocampo, Mena-Segovia, & Bolam, 2014). Furthermore, Cui, Jun, Jin *et al.* (2014) identified that activity in MSNs corresponding to both the direct and indirect pathways in mice are increased when actions are to be made, but not during rest.

The dual role of STR neurons is supported by gross changes in STR activity with adjustments in response thresholds. Increased activity in the pre-SMA and STR has been found when participants are cued to respond with speed, and variations in activation are associated with the ability to arbitrate between different response thresholds (Forstmann *et al.*, 2008). Indeed, better ability is related to stronger structural connectivity between the pre-SMA and STR (Forstmann *et al.*, 2012). Jahfari, Waldorp, van den Wildenberg *et al.* (2011) have also identified different activation patterns between cortical regions and sub-divisions of the STR in slow vs. fast inhibitors in the Simon task[17]. While fast inhibitors demonstrate increased connectivity between the rIFG and putamen, slow inhibitors demonstrate increased connectivity between the pre-SMA

[17] A choice reaction time task in which participants are required to identify a stimulus presented either to left or right of fixation. The location and the key to be responded with can either be consistent (response and target presented on either the left or right) or inconsistent (response presented on the left and target on the right or vice-versa).

and caudate. Importantly the strength of the connections from the rIFG and pre-SMA to the caudate was negatively correlated and may be indicative of different inhibitory strategies in slow vs. fast inhibitors. These findings indicate that STR neurons may be differentially responsive to reactive and proactive inhibitory requirements. The relationship between slow and fast inhibitors is in-keeping with the possibility that the STR supports evidence accumulation (Jahfari, Waldorp, Ridderinkhof, & Scholte, 2015), and is the 'default' system that requires release when enough information is acquired for an appropriate response is to be made (Criaud, Wardak, Hamed *et al.*, 2012). The STR has also been proposed to set the "point of no return"- i.e. the border between controlled processes that can be modulated, and ballistic stages that once initiated cannot be changed (Schmidt *et al.*, 2013). If such a point exists, it is likely very short (Verbruggen & Logan, 2009a) and thus likely associated with activation of either the direct (response execution) or indirect neurons (response inhibition) in the STR. The adjustment of response thresholds can also be observed down-stream, where reduced effective connectivity between the pre-SMA, STR and STN is observed with lower thresholds (Jahfari *et al.*, 2015).

1.2.3.2. The subthalamic nucleus

In the response inhibition literature, a dominant position is that reactive inhibition of a prepotent response tendency is achieved via direct cortical projections to the STN (e.g. Aron & Poldrack, 2006; Aron *et al.*, 2007). The STN has been found to be structurally connected to motor functions in both animals (Haynes & Haber, 2013) and humans (Middleton & Strick, 2000) and its activity has been found to correlate with SSRT (Aron & Poldrack, 2006). Furthermore, the application of deep brain stimulation (DBS[18]) to the STN in PD has been found to improve SSRT (Mirabella, Iaconelli, Romanelli *et al.*, 2012; Swann et al., 2011; van den Wildenberg, vam Boxtel, van der Molen *et al.*, 2006, although not always: Obeso *et al.*, 2013; Ray, Jenkinson, Brittain *et al.*, 2009).

Aron & Poldrack (2006) propose that top-down control of the STN in implementing response inhibition originates in the rIFG. Using fMRI they observed elevated activity within the right IFG, pre-SMA, GP and STN when participants were

[18] Deep brain stimulation involves the application of small, rhythmic electrical currents direct to basal ganglia targets (typically STN, GP or SN) via implanted electrodes (Lozano, Dostrovsky, Chen & Ashby, 2002).

required to inhibit responses in the SST. Correlations between activity in the rIFG and STN with SSRT were observed and greater activity was found in fast vs. slow inhibitors (as indexed by short vs. long SSRTs respectively; although the opposite relationship was identified by Li, Yan, Sinha & Lee, 2008). No such relationships were found in relation to the pre-SMA or GP. Aron & Poldrack (2006) argue that the co-activation (and correlation) of rIFG and STN activity is indicative of a specialised response inhibition network. This possibility is supported by anatomical connectivity between the rIFG, STN and pre-SMA (Aron *et al.*, 2007; Figure 1.17a). Furthermore, effective connectivity between the rIFG, pre-SMA and BG appear stronger when rapid reactive control is required (Jahfari *et al.*, 2012).

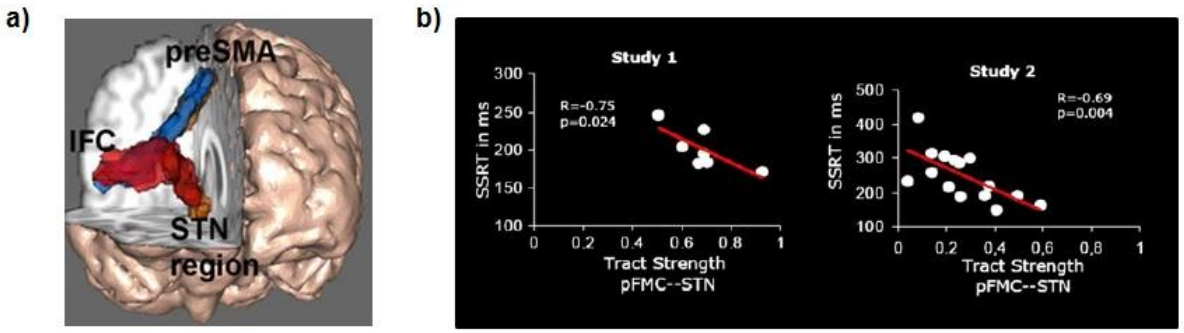

Figure 1.17. (a) Illustrates the white matter connectivity between the pre-SMA, IFC and STN as identified using diffusion weighted imaging. Image from Aron *et al.* (2007). **(b)** The relationship between white matter tract strength connecting the posterior medial frontal cortex (pMFC) and the STN with SSRT. Image from Forstmann *et al.* (2012).

If a specialised response inhibition network exists then it would be expected to be supported by regions crucial for conflict monitoring. As discussed above, the ACC has been argued to react to response errors (e.g. Dimoska *et al.*, 2006; Jodo & Kayama, 1992; Menon *et al.*, 2001; Senderecka *et al.*, 2012) and may assist the STN in implementing response inhibition (Forstmann *et al.*, 2012; see also Keuken, van Maanen, Bogacz *et al.*, 2015). White matter strength between ACC and STN has been found to be predictive of SSRT, with stronger connections related to increased efficiency of inhibitory control (Figure 1.17b; Forstmann *et al.*, 2012). Furthermore, activity in the ACC and STN correlate with increasing response options (Keuken *et al.*, 2015) and suggest the ACC may be recruited as task demands increase.

When multiple response options are available, the STN may act as a 'brake' (Frank, 2006) allowing time for the accumulation of evidence to ensure an appropriate response is made (Keuken *et al.*, 2015). The potential for the STN to influence speed-accuracy tradeoffs is supported by PD patients who exhibit faster goRTs and increased commission errors after subthalamatomy or when DBS is applied to the STN (Antoniades, Bogacz, Kennard *et al.*, 2014) - a finding mirrored in rat studies subsequent to STN lesion (Eagle *et al.*, 2008). The possibility that the STN acts as 'pause' in decision making rather than the outright stopping of actions is consistent with recent work that has established similar STN activity in the SST regardless of whether stop signals are successfully inhibited or not (Schmidt *et al., 2*013) and the observation that STN activity does not change under conditions of intentional response inhibition in either children or adults (Schel *et al.*, 2014). Eagle *et al.* (2008) posit that the STN may trigger the stop processes, rather than implementing it directly. The STN is known to project to the SN and which could be the origin of the stop process. Consistent with this possibility, Schmidt *et al.* (2013) established neurons in the rat SN (specifically the *pars reticular*) to significantly increase their firing rate during successful, relative to unsuccessful, stop signals[19]. Furthermore, activity in the STN has been found to initiate at approximately 15ms post-cue onset and thus is unlikely to be due to the reception of cortical projections (Schmidt *et al.*, 2013).

As discussed, the role of the BG in response inhibition has largely concentrated on the activity of the two hypothesised input stations, the STR and the STN. While the STR has been argued to be involved in proactive response inhibition and the STN in reactive inhibition, evidence indicates they may also sustain processes that are not necessarily inhibitory. Specifically, both regions have been proposed to set and adjust response thresholds, with the STR determining the point between controlled and ballistic stages of response execution, and the STN modulating evidence accumulation prior to a decision. Furthermore, the STN has been found to be anatomically and functionally related to the ACC and thus may play a role in resolving response conflict. Exploration of the BG beyond the STR and STN is required to establish whether there is a subcortical mechanism specialised to the implementation of response inhibition.

[19] The STN is also known to project to the GPi (Figure 1.15), but this is less likely to be the source of the stop process as Schmidt *et al.* (2013) identified minimal differences in GP activity on successful vs. unsuccessful stop trials.

1.3. Response inhibition at the neurochemical level

Much neuroscience focuses on the investigation of the interaction between specific neurons and their role in information processing (Aron, 2007). Here, I limit this area of discussion to the potential role of neurotransmitters in response control. Previous work has largely focused on the role of monoamines (serotonin, dopamine and noradrenalin) but recent evidence has highlighted a potential role for the inhibitory neurotransmitter γ-Aminobutyric Acid (see Hayes, Jupp, Sawiak *et al*., 2014, for a review). Here, I provide a brief overview of the literature with regards to these neurotransmitters and how this relates to our understanding of the biochemical basis of response inhibition.

1.3.1. The role of monoamines in response inhibition

The work of Soubrié, (1986) prompted interest into the role of serotonin (5-HT) in impulsivity and response control. In a review paper Soubrié argues that while 5-HT is released upon the presence of anxiety-inducing stimuli, its role is not to reduce anxiety but to enhance response control. This position was based on the observation that depleted 5-HT levels in animal SN increased response execution tendencies. Furthermore, such tendencies were more pronounced when response conflict was induced by simultaneous stop and go requirements. This has since been supported by a number of animal and human studies (see Aznar & Hervig, 2016, for a recent review). Lesions of the raphe nuclei (the brainstem origin of serotonergic projections; Lidov & Molliver, 1982) and the use of selective 5-HT reuptake inhibitors (SSRIs) in mice has been found to impair performance on tasks requiring response withholding (e.g. Thornton & Goudie, 1978; Eagle *et al.,* 2009). In autism, tryptophan depletion[20] has been found to improve go/no-go performance with concurrent modulation of fronto-thalamic activity (Daly, Ecker, Hallahan *et al.*, 2014). Furthermore, polymorphisms of genes crucial to the production of 5-HT have been found to modulate bilateral IFG activity (Ruocco, Rodrigo, Carcone *et al.*, 2016; see also Section 1.2.1). However, the influence of 5-HT on inhibition as required in the SST is unclear. SSRT is unaffected by 5-HT modulation by SSRIs or tryptophan depletion in both animals and humans (Clark,

[20] The consumption of a beverage containing all amino acids except tryptophan reduces tryptophan levels in blood plasma and ultimately reduces 5-HT levels in the brain (Young, Smith, Pihl, & Ervin, 1985).

Roiser, Cools *et al.,* 2005; Crockett, Clark, & Robbins, 2009; Eagle *et al.*, 2009; Nandam, Hester, Wagner *et al.,* 2011).

While these studies indicate 5-HT may support action restraint and not action cancellation (as suggested by Eagle *et al., 2*008), this is at odds with recent work by Ye *et al.* (Ye, Altena, Nombela *et al.*, 2014a, 2014b; Ye, Rae, Nombela *et al.*, 2016) who found improvements in inhibitory control (in both SST and go/no-go task) in patients with PD who used SSRIs. Improved frontal activity during response inhibition was observed with SSRI use, and appeared dependent on the strength of prefrontal-STR connectivity. It is possible that the discrepancies between this and previous work may be associated with differential roles of 5-HT in health and disease. There may well be variation in baseline levels of 5-HT between clinical and non-clinical groups as well as differential interactions between 5-HT and other neuromodulators. Specifically, in PD observed serotonergic modulation may be dependent on its interaction with dopamine (DA) - a neurotransmitter known to be depleted in this disorder (Calne & Langston, 1983; Scatron, Javoy-agid, Rouquier *et al.,* 1983).

DA has long been implicated as the source of neuromodulatory dysfunction in addictive behaviours (including pathological gambling, drug and alcohol addiction and, more recently, overeating; e.g. Dawe, Gullo, & Loxton, 2004; Volkow, Fowler, Wang *et al.,* 2009; Zack & Poulos, 2009) and various psychological and neurological disorders (including schizophrenia, PD and ADHD: Fusar-Poli, Rubia, Rossi *et al.,* 2012; Mcgowan, Lawrence, & Sales, 2004; O'Sullivan, Wu, Politis *et al*., 2011). The role of DA in action control is supported by findings in patients with ADHD. Impairments in response inhibition are hallmark of ADHD and symptoms are thought to be associated with low DA levels which modulate STR function (e.g. Fusar-Poli *et al.,* 2012). Reduced fronto-STR activity under conditions of response inhibition is typically observed in unmedicated ADHD relative to healthy controls (Vaidya *et al.,* 1998; see also Rubia, Alegira, Cubillo *et al.,* 2014) and is up-regulated with selective DA reuptake inhibitor (SDRIs; e.g. methylphenidate; Rubia, Halari, Mohammad *et al.*, 2011) use. The number of available DA transporters in medicated ADHD participants is greater than in medication-naive ADHD participants (see meta-analysis by Fusar-Poli *et al., 2*012) and may be key to the normalisation of fronto-STR activity with SDRI use. This is supported by work showing that variations in genes known to encode for DA transporters can predict STR activity (Cummins, Hawi, Hocking *et al.,* 2012). Furthermore, methylphenidate-enhanced fronto-STR activity has also been found to

correlate with SST performance in ADHD (Vaidya *et al.,* 1998; Rubia *et al.,* 2014). Similar behavioural modulation has been demonstrated in mice with SDRI and DA agonsit use (e.g. Bari, Mar, Theobold *et al*., 2011; Humby, Eddy, Good *et al.,* 2013). However, in healthy participants differential patterns of behavioural perfromance and fronto-STR activity after SDRI use is evident (e.g. see conflicting results from Costa et al., 2013; Nandam *et al.,* 2011; Sheridan, Hinshaw, & D'Esposito, 2010; Vaidya *et al.,* 1998). As such, it has been argued that DA is involved in processes associated with response inhibition tasks that may not involve the cancellation of ongoing actions *per se*.

In particular, DA is known to be important in the processing of rewarding and punishing stimuli and it has been proposed that its role in response inhibition is involved in error monitoring (Holroyd & Coles, 2002). As mentioned, the ACC is particularly responsive to the execution of incorrect responses and negative feedback (e.g. Dimoska *et al.,* 2006; Jodo & Kayama, 1992; Senderecka *et al.,* 2012; Emeric *et al., 2*011; Menon *et al.,* 2001) and the use of methylphenidate in ADHD is known to increase activity within this region (Rubia, Halari, Mohammad *et al.,* 2011; Rubia, Smith, Brammer *et al.,* 2005). Active blocking of DA receptors in rats has also been found to improve post-error slowing in the SST (Bari & Robbins, 2013b) and methylphenidate in healthy participants has been found to increase STR activity in expectation of a stop signal (Manza, Hu, Ide *et al.,* 2016). In addition, DA is elevated under go/no-go task, relative to SST, conditions (Costa *et al.,* 2013). While it is possible that this reflects a difference in action restraint vs. action cancellation (see Figure 1.1 and Section 1.2.1.1), Costa *et al.* (2013) argue this distinction is the result of increased error salience in go/no-go tasks, as commision errors are less frequent than in the SST. The role of DA in response inhbition has also been questioned in PD. Evidence suggests the motor symptoms of PD are associated with DA diminution within the SN (Calne & Langston, 1983; Scatron *et al.,* 1983) but drugs known to elevate BG DA seldom improve symptoms (Ye *et al.,* 2014a, 2014b, 2016) and do not enhance SST performance (Obeso *et al.,* 2011). Consequently, researchers have been motivated to explore the role of alternative neuromodulators in response inhibition.

Noradrenalin is a relatively under-researched monoamine, relative to 5-HT and DA. But while 'young', evidence is largely supportive and interest is growing (Eagle *et al.,* 2008; see Chamberlain & Robbins, 2013, for a review). Selective NA reuptake inhibitors (SNRIs, e.g. atomoxetine) have been found to improve SSRT performance in

rats (Bari, Mar, Theobald e*t al.,* 2011; Bari & Robbins, 2013b), healthy humans (Chamberlain, Hampshire, Müller *et al.,*2009; Chamberlain, Müller, Blackwell *et al.,* 2007), participants with ADHD (Chamberlain, del Campo, Dowson *et al.*, 2007) and patients with PD (Ye *et al.*, 2014b, 2016). Furthermore improvements in SSRT with atomoxetine use have been found to correlate with improvements in rIFG activity in ADHD (Chamberlain *et al.,* 2009). Direct comparison of the effects of different monoamine reuptake inhibitors in rats have established atomoxetine to improve SSRT while SSRIs and SDRIs have been found to influence general RTs (Bari *et al.,* 2011; Eagle *et al.,* 2009). Although note, atomoxetine also increases the time to complete tile-turning tasks in PD participants and thus may act to increase response thresholds (Kehagia, Housden, Regenthal *et al.*, 2014).

In PD, the degeneration of the locus coeruleus is associated with a loss of NA projections to the frontal cortex, particularly to the rIFG, pre-SMA, DLPFC and ACC (Braak, Rub, Gai, & Del Tredici, 2003). Dysfunctional connectivity may explain the corresponding reduction in activity in these regions during response inhibition tasks (Chamberlain & Robbins, 2013). Atomoxetine has been found to increase functional connectivity between rIFG and ACC in PD patients under 'task-free' conditions (Borchert, Rittman, Passamoni *et al.,* 2016) and thus, like DA may be associated with normalising error monitoring. This SNRI has also been found to elevate rIFG activity when responses are successfully inhibited on stop signal trials in healthy participants (Chamberlain *et al.,* 2009) and those with PD (Ye *et al.,* 2014a). Ye *et al.* (2016) also demonstrated that SSRT performance subsequent to atomoxetine use in PD can be predicted by a model inclusive of the STR, pre-SMA and rIFG- with a rate of approximately 85%. Furthermore, this model was also able to predict inhibitory performance subsequent to citlopram (an SSRI) use to a similar extent. The authors suggest that this commonality may be indicative of multi-monoamine transmission supporting response inhibition. Importantly, as mentioned, the role of 5-HT may be disease dependent and was found to better reduce SSRT in more advanced PD (Ye *et al.,* 2016).

Collectively, this brief overview indicates that monoamine activity is largely influential in the SST. However, it is unlikely that the role of 5-HT and DA is specific to the cancellation of action plans. DA may act to support non-inhibitory processes such as performance and error monitoring and 5-HT may exert its effects differently dependent on disease state. While the evidence thus far is particularly encouraging for a

specific role of NA in supporting fronto-STR activity under SST conditions, more work is needed to establish its role in setting response thresholds and other aspects of inhibitory control. Evidence is also mounting to support the other neurochemicals in response control, specifically in favour of the principle inhibitory neurotransmitter γ-Aminobutyric Acid (Buzsáki, Kaila, & Raichle, 2007; Isaacson & Scanziani, 2011).

1.3.2. γ -Aminobutyric acid

γ -Aminobutyric acid (GABA) comprises approximately 20-25% of all synaptic connections in the human nervous system (Buzsáki *et al.*, 2007; Isaacson & Scanziani, 2011) and, along with glutamate, is essential for the maintenance of the balance between excitation and inhibition within the brain (Buzsáki *et al., 2*007; Isaacson & Scanziani, 2011). The inhibitory influence of GABA is realised postsynaptically by the increase of chlorine flux across the cell membrane. This results in hyperpolarisation and a reduction in the susceptibility of the neuron to respond to excitatory input (Buzsáki *et al.*, 2007; Maffei, 2011). GABA is proposed to support neural plasticity, specifically of motor control (Bachtiar & Stagg, 2014; Blicher, Near, Naess-Schmidt *et al*., 2015; Paik & Yang, 2014), with concentrations decreased in healthy humans under conditions of motor learning (Floyer-Lea, Wylezinska, Kincses, & Matthews, 2006). In stroke patients, GABA concentrations dip subsequent to infarct and have been proposed to maintain or enhance motor function (Bachtiar & Stagg, 2014; Blicher *et al.*, 2015; Paik & Yang, 2014). Furthermore, GABAergic/glutamatergic projections between nuclei comprising the putative BG pathways are crucial for response control (Figure 1.16; Albin *et al.*, 1989; Alexander & Crutcher, 1990; Nambu, *et al.*, 2002; Section 1.2.3) and the injection of GABA agonists into motor areas of monkey brains impairs the execution of sequences of movements (Lu & Ashe, 2005; Shima & Tanji, 1998). Thus, while neuronal and behavioural inhibition are not equivalent (Aron, 2007), it is possible that GABA may act to support different forms of motor control and may be influential in stopping behaviour (see Hayes *et al.*, 2014, for a recent review). Given the abundance of GABAergic neurons within the brain, it is likely this neurotransmitter acts to support non-inhibitory as well as inhibitory processes.

As mentioned, the motor symptoms associated with PD are argued to be the result of DA depletion in the SN (Calne & Langston, 1983; Scatron *et al.*, 1983). This depletion may have a ‘knock-on’ effect to the excitatory-inhibitory balance in the BG

(Bahuguna, Aertsen, & Kumar, 2015; Calabresi *et al.*, 2014). DA from the SN acts to modulate the sensitivity of GABA receptors in the STR (Yager, Garcia, Wunsch, & Ferguson, 2015), by way of GABAergic MSNs which comprise 95% of all neurons within the STR (Calabresi *et al., 2*014). The reduction in DA in PD therefore exerts an indirect effect on GABAergic projections from the STR to other BG nuclei, for which the net effect is decreased thalamico-cortico output. Thus while PD is classically conceptulised as a disorder of response execution it can also be described as a disorder of excessive inhibiton (Jahanshahi *et al.*, 2014).

Motor symptoms of PD can be alleviated by DBS when applied to BG nuclei (see Bronstein, Tagliati, Alterman *et al.*, 2011; Lozano, Dostrovsky, Chen, & Ashby, 2002; for reviews), and although the the mechanisms by which DBS exerts its effects are unclear, they may be GABAergic[21]. DBS to the GPi, STR in animals have been found to increase local GABA concentration (Melon *et al.*, 2015; Chiken & Nambu, 2013). In humans, DBS to the STN reduces GABA in the THAL (Bronstein et al., 2011), while also improving stopping performance (van den Wildenberg et al., 2006; Georgiev, Dirnberger, Wilkinson *et al.*, 2016). However, DBS has been found to increase commission errors on go/no-go tasks (Hershey, Revilla, Wernle *et al.*, 2004) and improve the speed of responding on go trials, with no effect on SSRT (Kohl, Aggeli, Obeso *et al.*, 2015). The benefits of DBS may therefore be driven by faster response selection and lower response thresholds (Kohl *et al.*, 2015; Pote, Torkamani, Kefalopoulou *et al*., 2016) as opposed to improved inhibitory control (see also Section 1.2.3). However, the BG targets of DBS in these studies differ and likely contribute to these reported discrepancies. Additional interplay between regions beyond that proposed by the classic pathways models (Albin *et al.*, 1989; Alexander & Crutcher, 1990; Nambu *et al.*, 2002) also require consideration. For example, recent rat work has shown specific GABAergic projections from the GPe to the STR, activate under stop relative to go conditions (Mallet, Schmidt, Leventhal *et al.*, 2016).

Further evidence for GABAergic support of response control is available from studies using TMS, particularly those that involve short or long interval intracortical inhibition (SICI/LICI). When a supra-threshold test TMS pulse is applied shortly after a sub/supra-threshold conditioning TMS pulse (2-4ms for SICI, and 50-200ms for LICI,

[21] Similar reductions in motor symptoms have also been found after the insertion of GABA releasing cells into the SN of rats (Carlson, Behrstock, Tobin & Salamone., 2003).

respectively) there is a subsequent reduction in the response to the test pulse (Chen, 2004; Lazzaro, Resuccia, Oliviero *et al.,* 1998; Rothwell, Day, Thompson, & Kujirai, 2009). This effect is the result of the test pulse being administered at a point where pyramidal neurons are under GABAergic influence. SICI is thought to reflect the activity of $GABA_A$ neurons, whereas LICI is thought to reflect the activity of $GABA_B$ neurons (Rothwell, Day, Thompson, & Kujirai, 2009). In no-go situations, activity in hand muscles is further reduced by a test TMS pulse when applied to the primary motor cortex (M1) relative to controls. This reduction has been found at both short and long interval latencies, where the maximum suppression of muscle activity has been found at 2ms and 80ms after the test pulse, respectively (Sohn, Wiltz, & Hallett, 2002; Waldvogel, van Gelderen, Muellbacher *et al.,* 2000). In SST, reduction in muscle activity during the cortical silent period (the duration in which involuntary muscle contraction is interrupted by TMS to the contralateral motor cortex) has been found approximately 134ms after the test stimulus (van den Wildenberg, Burle, Vidal *et al.,* 2009). The time variation in suppressive effects of a test pulse under no-go and stop signal conditions may be indicative of differences in GABAergic activity supporting action restraint and action cancellation. Patients with ADHD and PD also show reduced TMS-induced SICI and LICI effects (e.g. Bareš, Kaňovský, Klajblová, & Rektor, 2003; Gilbert, Isaacs, Augusta *et al.,* 2011; Siebner, Mentschel, Auer *et al.,* 2000), further supporting the potential importance of GABA in response control.

Collectively, the investigation of GABA in response inhibition appears a worthwhile endeavour. Previous research with humans has proven challenging due to the inability of GABA to cross the blood-brain barrier (Boonstra, Kleijn, Colzato *et al*., 2015), and work has had to focus on the influence of disease and animal studies. However, advancements in imaging techniques have made the quantification of GABA *in vivo* possible (Puts & Edden, 2012) and provide exciting avenues for future investigation. Indeed, such techniques have already enabled relationships between GABA, impulsivity and motor control (e.g. Boy, Evans, Edden *et al.,* 2010; Boy, Evans, Edden *et al.,* 2011; Draper, Stephenson, Jackson *et al.,* 2014; Silveri, Sneider, Crowley *et al*., 2013) to be identified, as well as those between subcortical GABA concentration and go/no-go task perfromance (Quetscher, Yildiz, Dharmadhikari et al., 2014).

1.4. Why pre-registration?

The recent publication of Nosek *et al.*'s "estimating the reproducibility of psychological science" (2015) has been met with claims that psychological science is in the midst of a 'reproducibility crisis'. Even though this assertion is heavily debated (c.f. Anderson, Bahník, Barnett-Cowan *et al*., 2016; Gilbert, King, Pettigrew, & Wilson, 2016), it is of great concern that findings were replicated for only a little over a third of the studies repeated by Nosek *et al.* (2015). Although topical, poor reproducibility is by no means a modern dilemma (e.g. de Groot, 1956; Rosenthal, 1979) and the 'publish or perish' culture of scientific research generally has been argued to be at the heart of the issue (Asendorpf, Conner, De Fruyt *et al.*, 2013; Fanelli, 2010; Fang, Steen, & Cadadevall, 2012). The tendency for publishers to favour significance and novelty over replication and null findings (Brembs, Button, & Munafò, 2013; Ferguson & Heene, 2012; Masicampo & Lalande, 2012; Rosenthal, 1979; Vasilev, 2013) may have led researchers to participate in questionable research practices (e.g. *p*-hacking, HARKing and biased reporting[22]; Masicampo & Lalande, 2012; Fang *et al.*, 2012; see also John, Loewenstein, & Prelec, 2012). While a number of positive movements have arisen over the past few years to aid transparency in science (e.g. calls to reward replication studies, the Open Science Framework– https://osf.io/ –and the open fMRI project; Poldrack, Barch, Mitchell *et al*., 2013; Wagenmakers & Forstmann, 2014), study pre-registration has been identified as key (Asendorpf *et al.*, 2013; Chambers, 2013). As such, the methods, hypotheses and statistical approaches adopted for the largest studies presented in this thesis were pre-registered under the Open Science Framework prior to data collection (https://osf.io/zbk3p/ and https://osf.io/4z7pu/). These pre-registered studies both include the use of imaging techniques, for which the estimated incidence of false positives (i.e. the detection of an effect that is not real: type I error) and potential for researcher degrees of freedom is particularly high (Carp, 2012; David, Ware, Chu *et al.*, 2013; Wager, Lindquist, Nichols *et al.*, 2009). Carp (2012) demonstrated that in a typical fMRI study (here, Aron *et al.*, 2007), over 34,000 different statistical maps could be generated from the adjustment of just 5 pre-processing steps and 5 modelling decisions. Consequently, there is more than ample opportunity to interrogate imaging

[22] *p*-hacking involves data mining to reveal statistically significant results. HARKing involves the recreation of hypotheses to fit with research findings. Examples of report bias include undisclosed analytic flexibility and reporting only statistically significant results.

data to obtain desired results[23]. To further increase the transparency of my research, I also plan to make all data and analysis scripts available upon publication.

As the fields of neuroscience and psychology progress towards more 'open' research practices, there is also a simultaneous move towards the use of more informative statistics than the Frequentist approaches traditionally adopted. The merits of Bayesian statistics, which are reported throughout this thesis, are discussed in the next section.

1.4.1. Bayesian statistics

Statistical power is an important concept in scientific research to ensure the detection of true effects (Cohen, 1988, Cohen, 1992a, 1992b). However, Button, Ioannidis, Mokrysz *et al.* (2013) established that in neuroscience the statistical power of published work is approximately 20%, far below the recommended minimum of 80% (Cohen, 1992a, 1992b; Cohen, 1988)[24]. This means that if 100 studies were conducted and true effects were present in them all, only 20 would produce statistically significant results (i.e. there is a high probability of obtaining a false negative–type II error–Button *et al.*, 2013). The problem with low statistical power extends beyond the possibility of not detecting effects and can also contribute to the presence of type I error (Button *et al.*, 2013; Masicampo & Lalande, 2012; Fanelli, 2010; Wager *et al.*, 2009; Simmons, Nelson, & Simonsohn, 2011). Consequently, research findings are rendered unreliable. As such, analytic techniques that do not rely heavily on statistical power may provide suitable alternatives to establishing whether or not a hypothesis is supported.

Unlike null-hypothesis significance testing, Bayesian inferential methods allow us to establish the confidence that can be placed in our experimental hypothesis given the data (H_1; that there is an effect of the experimental manipulation on dependent measures) vs. the null hypothesis (H_0; that there is no effect of the experimental manipulation on dependent measures). This can be expressed as a ratio, known as a Bayes Factor (BF):

[23] Studies 3 and 4 were not pre-registered prior to data collection. These studies were largely exploratory (as opposed to confirmatory) and were conducted to provide insights into task development for future work. The results from these studies may be used as pilot data for future studies.
[24] Although this problem is not limited to neuroscience (e.g. see Jennions & Møller, 2003).

$$BF_{10} = \frac{\text{likelihood of data given } H_1}{\text{likelihood of data given } H_0}$$

The resulting BF can range from 0 to infinity, where BF>1 provides evidence for H_1, and BF<1 provides evidence for H_0. A BF of ~1 suggests limited sensitivity of the experiment to detect effects (Zoltan Dienes, 2014). However, to infer 'substantial evidence' for H_1, BF>3 would be expected, while BF<1/3 would provide 'substantial evidence' for H_0 (Jeffreys, 1961). Thus, BFs are particularly helpful for the interpretation of null findings (Dienes, 2011, 2014; Rouder, Speckman, Sun *et al.*, 2009). Furthermore, BFs are not susceptible to type I and type II error. As such, there is no requirement to correct for multiple comparisons (Dienes, 2011, 2014; Rouder *et al.*, 2009) [25] and Bayesian tests allow for a flexible stopping rule where additional data can be collected if necessary without the need to correct for the increased type I error (Dienes, 2011, 2014).

The calculation of BF requires some knowledge of *prior odds*; the relative probability of H_1 relative to H_0 before the investigation. Prior odds can based on previous research findings (Dienes, 2011, 2014) or can be objective. To prevent the use of improper priors (which are based on the subjective decision of what constitutes 'evidence'), a 'default' prior (namely the JZS prior, Jeffrey-Zellner-Siow prior; Rouder *et al.*, 2009; Wetzels & Wagenmakers, 2012) is used for the majority of Bayesian analyses presented in this thesis.[26]

1.5. Synopsis

The overall aim of this thesis was to explore the role of non-inhibitory processes in response inhibition. To investigate, I combined neuroimaging and neurostimulation methods with the context-cueing paradigm (Verbruggen & Logan, 2009c; Verbruggen *et al.*, 2010) to explore behaviour, neurophysiology and neurochemistry during action updating in the presence and absence of inhibition. Thus, it was possible to control for

[25] It is important to note that BFs are not completely immune to issues relating to multiple comparisons as found in null hypothesis testing. While the results of Bayesian analyses are constrained by the information contained within the prior (i.e. that regarding a particular hypothesis), like *p*-values, BFs can fluctuate with sample size and are variable across analyses (when the same prior is used for multiple tests). Thus, it is theoretically possible to obtain a false positive result with Bayesian testing.

[26] Although note, there are instances where informed priors (Dienes, 2011, 2014) are used in addition to the JZS prior. Where applicable, these are fully explained.

several non-inhibitory processes that have been highlighted as important for SST performance. Attentional processes, including signal monitoring and signal detection, and the updating of an action plan as a means to achieve goal-directed behaviour, are controlled for throughout Studies 1-4. However, as will be discussed, the control for *all* possible non-inhibitory processes (including error processesing, conflict monitoring and conflict resolution) required in the SST is challenging, and potential methods to overcome these are presented in Study 4.

In Study 1 (Chapters 2-3), fMRI was used to reveal lateralised activity at both the cortical and subcortical levels under conditions of response inhibition and non-inhibitory action updating. Different response control conditions were found to recruit both overlapping and diverse regions of activity. Specifically, activity in the anterior rIFG, the *pars triangularis*, was uniquely associated with the requirement to inhibit a response. This specificity continued downstream to subcortical loci, where the pattern of activity in sub-structures of the BG largely confirmed the hypothesised putative pathways (Section 1.2.3). Importantly, left-hemisphere BG activity were recruited when participants were required to execute a response, and right-hemisphere structures were recruited when participants were required to inhibit a response.

In Study 2 (Chapters 4-5), I explored the effect of applying continuous theta burst stimulation (cTBS; a variant of TMS known to reduced cortical excitability for approximately 1 hour; Huang *et al., 2*005) to the rIFG on behavioural indices of action updating, BOLD signal and GABA concentration. Baseline relationships between the latency of the stop process with rIFG, GABA and BOLD proved inconclusive. Furthermore, I found no substantial evidence for a cTBS-induced modulation in any of the dependent behavioural measures and did not influence BOLD activity in remote cortical and subcortical regions known to comprise the response control network. Under baseline conditions, the specificity of the *pars triangularis* in response inhibition was upheld. However, this study also revealed a large region of the *pars opercularis* recruited exclusively when response inhibition was required, indicating the presence of a specialised inhibitory node. A partial replication of the lateralised BG activity associated with different action updating requirements established in Study 1 was also found.

In Study 3 (Chapter 6) I investigated whether the disparities in BOLD activity under conditions of inhibitory and non-inhibitory action updating could be explained by

task differences. Although an indirect indication, self-report ratings of task-related difficulty and frustration imply that cancelling an ongoing response may be more demanding than action updating in the absence of inhibition.

In the final study (Chapter 7) I propose a new paradigm that aims to overcome the need to estimate SSRT based on mathematical models (primarily the independent horse-race model), by the provision of a direct measure of the latency of the stop process. The advantages and disadvantages of this paradigm over the standard SST and context-cueing paradigm are also discussed.

Collectively, the findings presented in this thesis indicate the presence of a common network involved in supporting both inhibitory and non-inhibitory processes, with specialised activity associated with inhibitory control in both frontal and subcortical regions. However, this work also highlights the difficulties involved in, and the importance of, controlling for non-inhibitory processes in response inhibition research.

Chapter 2. Study 1, Part I

The neural correlates of inhibitory and non-inhibitory action updating

2.1. Introduction

The frontal lobe is thought to be central to the top-down control of actions (Miller & Cohen, 2001). Studies employing the SST and similar paradigms often point to the rIFG and pre-SMA as crucial to the implementation of motor inhibition (e.g. Aron *et al.,* 2003; Chambers *et al.,* 2006; Chambers *et al.,* 2007; Duann *et al.,* 2009; Zandbelt *et al.,* 2013; Li *et al.,* 2006; Floden & Stuss, 2006; Nachev *et al.,* 2007; Obeso, *et al.,* 2013), presumably by exerting influence over mid-brain functionality (Miller and Cohen, 2001; Aron *et al.,* 2006; Aron *et al.,* 2007; Duque *et al.,* 2007; Jahfari *et al.,* 2011). However, previous response inhibition research often fails to account for the possibility that these neural responses may also be observed in comparable situations involving action updating that do not require the cancellation of responses (Hampshire *et al.,* 2010; Dodds *et al.,* 2011; Chatham *et al.,* 2012; Erika-Florence *et al.,* 2014; Hampshire, 2015). As such, the extent to which the rIFG, pre-SMA and associated regions are specialised in their role in response inhibition is unclear.

The SST is amongst the most widely used paradigms in response-inhibition research. Participants are typically instructed to execute motor responses to stimuli on the majority of trials, but to cancel ongoing responses upon the presentation of infrequent, yet salient, signals (Logan & Cowan, 1984). The specificity of systems to motor inhibition can be appraised through comparison to control tasks in which actions are updated without response inhibition. One such paradigm is the DT (Verbruggen & Logan, 2009c; Verbruggen *et al.,* 2010). Here, stimulus presentation mimics the SST, controlling for confounds such as stimulus detection, but requires the execution of an additional response following the presentation of the infrequent signal rather than the inhibition of a response. Perceptual confounds have also been accounted for through the use of an additional task in which participants are instructed to ignore the infrequent signal. Collectively, these three tasks comprise the context-cuing paradigm (Verbruggen

& Logan, 2009c; Verbruggen *et al.*, 2010). This paradigm is employed in the current study (Figure 2.1).

Previous work aimed at specifying the functional relevance of nodes of the response control network has largely focused on the rIFG (e.g. Verbruggen *et al.*, 2010; Dippel & Beste, 2015; Hampshire *et al.*, 2010; Dodds *et al.*, 2011; Chatham *et al.*, 2012; Erika-Florence *et al.*, 2014). Recent findings show that this region may perform a general role in decision-making, even in the absence of overt cancellation of ongoing actions. For example, the application of TMS to the ventral rIFG has been found to impair both double-responding and inhibiting a response (Verbruggen *et al.*, 2010) as well as the execution of action sequences (Dippel & Beste, 2015). Imaging studies have also identified overlapping activity in the vicinity of the rIFG associated with action updating in both the presence and absence of inhibitory requirements (Hampshire *et al.*, 2010; Dodds *et al.*, 2011; Chatham *et al.*, 2012; Erika-Florence *et al.*, 2014; Hampshire, 2015; Hampshire & Sharp, 2015a, 2015b; see also Boecker *et al*., 2011; Mars *et al.*, 2007; Sharp *et al.*, 2010). In an attempt to disentangle the multiple cognitive processes involved in different forms of action control, the current study employs a context-cueing paradigm in combination with fMRI. The multiple aims and hypotheses of the study are outlined below and were registered prior to the collection of data (https://osf.io/zbk3p/). All analyses pertaining specifically to subcortical loci are reported in Chapter 3.

2.1.1. Primary aims

The primary pre-registered aim of this study was to establish the neuroanatomical distribution associated with inhibitory and non-inhibitory action updating, to test whether a unique prefrontal network supports response inhibition that is dissociable from that supporting non-inhibitory action updating. The focus of this study is on the differential activity of the rIFG and pre-SMA. Conjunction analyses were performed to establish which regions were recruited under both SST and DT conditions- overlapping regions of activity were indicative of the recruitment of general processes, not specific to either updating requirement. Differences between the SST and DT were isolated via disjunction analyses. Regions exclusively recruited under either SST or DT conditions indicate functional specialisation. Graded differences in activity across the tasks were identified through conventional contrast analyses. These analyses allowed me to explore

whether common regions of activity were recruited to different extents under different action updating conditions. Although the outcomes for this study were largely unknown, activity was anticipated to be in accord with previous research.

Right-lateralised fronto-parietal activity has been consistently observed in imaging studies employing response inhibition paradigms (e.g. Aron *et al.*, 2007; Aron & Poldrack, 2006; Cai & Leung, 2011; Kenner, Mumford, Hommer *et al*., 2010; see also reviews: Aron 2007, 2011; Banich & Depue, 2015), particularly in the rIFG and pre-SMA (e.g. Aron *et al.*, 2006, 2007; Li *et al.*, 2006, 2008). Similar fronto-parietal activity has been found in dual-task situations (e.g. (Collette, Olivier, Van Der Linden *et al.*, 2005; Dux et al., 2006, 2009; Erickson, Colcombe, Wadhwa *et al*., 2005; Heekeren, Marrett, Ruff *et al.*, 2006; Tombu, Asplund, Dux *et al*., 2011), but activation tends to be bilateral (or lateralised to the left), as opposed to being right lateralised (e.g. Collette et al., 2005; Herath, Klingberg, Young, Amunts, & Roland, 2001; Jiang, 2004).

More specifically, common activity was expected in the rIFG due to the overlapping activity observed in imaging studies employing both SST and DT (Hampshire *et al.*, 2010; Dodds *et al.*, 2011; Chatham *et al.*, 2012; Erika-Florence *et al.*, 2014; Hampshire, 2015; Hampshire & Sharp, 2015) and TMS-induced impairments in both inhibitory and non-inhibitory action updating (Verbruggen *et al.*, 2010; Dippel & Beste, 2015). Common activity in the DLPFC, ACC and medial frontal regions (such as the pre-SMA) was also expected as these sites are consistently activated across multi-task situations and in the SST (hypothesised to reflect the joint recruitment of working memory, performance monitoring, response selection and conflict resolution processes; e.g. Chikazoe *et al.*, 2009; Erickson *et al.*, 2005; Tombu *et al.*, 2011; Erika-Florence *et al.*, 2014; Hughes, Johnston, Fulham *et al.*, 2013; Sharp *et al.*, 2010). The detection of the infrequent signal required by all tasks comprising the context-cueing paradigm was also expected to be associated with regions commonly associated with attentional capture, namely the right inferior frontal junction (IFJ) and parietal regions (Corbetta & Shulman, 2002; Corbetta *et al.*, 2008; Chikazoe *et al.*, 2009; Verbruggen *et al.*, 2010; see also Sebastian *et al., 2*016). Definitive predictions regarding task-specific activity were not made.

2.1.2. Secondary aims

The secondary aims of the study were two-fold. First, I explored how the magnitude of blood oxygen level dependent (BOLD) activity associated with action updating in the SST and DT were related to measures of task performance and cognitive demands. Second, I explored whether it was possible to identify the neural correlates of the psychological refractory period (PRP; e.g. Telford, 1931; Welford, 1952; Pashler, 1994; Ruthruff *et al.*, 2003; Dux *et al.*, 2006) in the DT. Given clear evidence that regions previously implicated in response inhibition are not necessarily functionally specific to this process alone (Criaud & Boulinguez, 2013; see also Verbruggen *et al.*, 2014a; Mostofsky & Simmonds, 2008; Hampshire & Sharp, 2015a, 2015b), my work explored BOLD changes in multiple regions of interest (ROIs); including subcortical regions of the basal ganglia network theorised to be crucial to the implementation of response execution and response inhibition (subcortical analyses are reported in Chapter 3, Albin, *et al.*, 1989; Alexander & Crutcher, 1990; Nambu *et al.*, 2002; see Chapter 1, Section 1.2.3). Specific background information and hypotheses pertaining to each of these aims are summarised below.

2.1.2.1. Brain-behaviour relationships: inhibitory action updating

Activity in regions crucial to the implementation of action updating was expected to correlate with the latency of the corresponding behavioural process. In the SST, the latency of the stop process can be used to infer efficiency of inhibitory updating ability. Individuals with shorter SSRT exhibit superior inhibitory ability relative to those with longer SSRTs (Logan & Cowan, 1984; Verbruggen & Logan, 2009c). In previous research, the strength of connectivity between rIFG, pre-SMA, STR and STN have been related to the efficiency of response inhibition (Jahfari *et al.*, 2011; Forstmann *et al.*, 2012; Rae *et al.*, 2015). Furthermore, activation of the rIFG and STN have been found to negatively correlate with SSRT (Aron & Poldrack, 2006), and activation of medial and prefrontal cortices and the caudate[27] have been found to be greater in individuals with short vs. long SSRTs (Li *et al.*, 2006, 2008; see also Sharp *et al.*, 2010). It was therefore anticipated that participants who exhibited more efficient inhibitory control would demonstrate greater activity in such regions (although note, that some subcortical

[27] The striatum is the combination of the caudate and the putamen.

regions have been identified as more active in participants with long, relative to short, SSRTs; Li *et al.,* 2008).

Additionally, it was anticipated that regions crucial to updating performance would be differentially recruited as a function of task demands. In the SST, the SSD is adjusted to ensure successful inhibition occurs on ~50% of signal trials (Logan & Cowan, 1984). The probability of inhibitory success in the SST is greater when signals are presented at short SSDs (i.e. the signal is presented in close proximity to the stimulus) relative to longer SSDs (Logan & Cowan, 1984). Previous studies have identified correlations between activity in the right pre-SMA, GP and STN with SSD, where greater activity was found at longer delays (Aron & Poldrack, 2006; note, no correlation with rIFG activity was found).

2.1.2.2. Brain-behaviour relationships: non-inhibitory action updating

As outlined in Chapter 1 (Section 1.2.1.2), the PRP is a phenomenon observed in dual-task situations where the reaction time to a second stimulus is prolonged when presented in close temporal proximity to a first (e.g. Telford, 1931; Welford, 1952; Pashler, 1994; Ruthruff *et al.,* 2003; although this is not always the case, e.g. see Jiang, Saxe, & Kanwisher, 2004, for evidence of 'passive-queuing'). The PRP has been attributed to either a structural bottleneck limitation on dual-task processing (e.g. Pashler, 1994; Ruthruff *et al.,* 2003; Dux, et al., 2006, 2009; Tombu *et al.,* 2011; also see Marois & Ivanoff, 2005 for a review), or due to strategic serial postponement of responding to increase the ease and speed of processing in multi-task situations (e.g. Logan & Gordon, 2001; Meyer & Kieras, 1995, 1997a,1997b; Mille *et al.,* 2009; Schumacher & Lauber, 1999; Tombu & Jolicœur, 2003). It is therefore possible that the demands associated with action updating at short vs. long SOAs would lead to greater recruitment of the regions involved (either those that form a structural limitation or those that are involved the selection and sequencing of responses) as per previous work (e.g. Dux *et al., 2*006; Herath *et al., 2*001; Jiang, 2004; Szameitat, Schubert, Müller, & Von Cramon, 2002; but see Jiang *et al.,* 2004). Previous attempts to isolate the neural correlates of the central bottleneck have implicated a fronto-parietal network (e.g. Dux *et al.,* 2006, 2009; Collette *et al.,* 2005; Schubert & Szameitat, 2003; Szameitat *et al.,* 2002). Specifically, bilateral IFJ, IFG and pre-SMA have been pinpointed as potential loci of dual-task co-ordination (Collette *et al.,* 2005; Dux *et al.,* 2006, 2009; Herath *et*

al., 2001; Jiang, 2004; Marois, Larson, Chun, & Shima, 2006; Schubert & Szameitat, 2003; Sigman & Dehaene, 2008; Szameitat *et al.*, 2002; Tombu *et al.*, 2011), with left frontal regions implicated more frequently than right (e.g. Collette *et al., 2*005; Dux *et al., 2*009; Marois & Ivanoff, 2005). Dual-task studies often identify the bottleneck with respect to regions involved in dual minus single tasks, or regions which demonstrate greater activity at short vs. long SOAs (i.e. SOAs where the bottleneck is present vs. absent). In an attempt to define the locus (and size) of the central bottleneck I propose a novel method of delineating the magnitude and duration of the PRP within individual subjects. This method involves applying multiple fits to individual RT data over SOAs, as means to establish when RT is influenced by SOA, and when RT plateaus (i.e. when the PRP is no longer evident).

As noted above, my work explored BOLD changes in multiple ROIs (including subcortical regions of the BG network), and it was anticipated that ROIs would be recruited to different extents depending on the efficiency of individual non-inhibitory updating ability. As opposed to exploring the neural correlates of the PRP as noted above, here, I was interested in establishing the relationship between the efficiency of the non-inhibitory action updating latencies (measured by the onset of the additional response minus the onset of the signal; DRT2) and regional activity under DT conditions.

2.1.2.3. Lateralisation of function

In accord with previous research, right lateralised activity was anticipated in ROIs associated with the SST, and bilateral or left lateralised activity presented in ROIs associated with the DT (e.g. Aron, *et al., 2*007; Aron & Poldrack, 2006; Cai & Leung, 2011; Collette *et al., 2*005; Dux *et al.*, 2006, 2009; Erickson *et al., 2*005; Heekeren *et al.*, 2006; Kenner *et al.*, 2010; Tombu *et al., 2*011).

2.1.3. Exploratory aims

The current study also aimed to establish the patterns of activity within subcortical regions hypothesised to underlie response execution and response inhibition. These

analyses sought to establish whether activity under inhibitory and non-inhibitory action updating conformed to patterns predicted by the direct, indirect and hyperdirect pathways (Albin *et al.*, 1989; Alexander & Crutcher, 1990; Nambu *et al.*, 2002). These analyses and results are discussed in Chapter 3.

2.2. Methods

2.2.1. Participants

Of the 38 participants included in the study, 8 were excluded according to pre-registered criteria[28] (APP10.1.3). The final sample included 30 right-handed participants[29] (5 males, 25 females), aged between 18 and 29 years (M=21.43, SD=2.64). Participants had normal or corrected-to-normal vision, were neurologically healthy and screened for contraindications to MRI and TMS (Maizey, Allen, Dervinis *et al.*, 2013; see APP10.1.1 for relevant screening forms). Informed consent was received from each participant and all methods were approved by the School of Psychology Research Ethics Committee, Cardiff University. Participants were reimbursed at a rate of £10 per hour for their time (£45 in total). All participants completed a separate training and testing session (2 hours and 2.5 hours, respectively).

2.2.2. Behavioural task

The behavioural task consisted of an adapted version of the context-cueing paradigm employed by Verbruggen *et al.* (2010; Figure 2.1). Participants were instructed to respond the direction of a white arrow presented in the centre of a dark grey screen (visual angle = 1.75˚ x 3.69˚) for 1,250ms. Right index finger responses were required upon presentation of arrows pointing to the left (<<<) and right middle finger responses required to arrows pointing to the right (>>>). Participants were instructed to respond as

[28] Four participants were excluded due to poor behavioural performance (1 during training and 3 subsequent to the scan session), 1 due to excessive head motion during the scan session, 2 withdrew from the study of their own accord and 1 participant failed to meet safety guidelines required for TMS/MRI research.

[29] A total sample size of 30 was pre-specified and limited due to logistical constraints. This sample size is larger than related studies employing similar paradigms (typically between 14-20 participants; e.g. Chatham *et al.*, 2012; Dodds et al., 2011; Erika-Florence *et al.*, 2014; Hampshire *et al.*, 2010; Hampshire, 2015).

fast and as accurately as possible to ensure the development of a prepotent response tendency (Logan & Cowan, 1984). Signal trials occurred on 1/3 of trials; here, the arrow turned black for 250ms after a variable delay (see Section 2.2.2). After the signal duration, the arrow stimulus returned to white for the remainder of the trial. The presence of the signal informed participants to alter their response depending on a cue provided to them at the beginning of each block: STOP, DOUBLE or IGNORE (Figure 2.1).

Cues were presented in the centre of the screen for 7,000ms at the beginning of each task block. Across all three cue types it was emphasised that where responses had to be made, they should be made as fast and as accurately as possible (see APP10.1.3 for task instructions). Importantly, participants were instructed not to wait for a signal to appear and that responding to the direction of the arrow was their primary task. Participants were also advised that correctly stopping their response would be more difficult on some trials than on others and that errors were to be expected. Fixation crosses were presented prior to each stimulus and formed the inter-trial interval (ITI; Visual angle = 1.75˚ x 1.75˚). The duration of the ITI was pseudo-randomly jittered between 500ms, 1,000ms and 2,000ms, but occurred with equal probability within each task block. The block design for the training and scan sessions differed and are outlined in Sections 2.2.3 and 2.2.4, respectively.

The behavioural task was programmed using Psychophysics toolbox in MATLAB (www.psychtoolbox.org; Mathworks, Natick,MA; Brainard, 1997). All stimuli were presented in the centre of a screen set to a refresh rate of 60Hz (resolution of 1024x768 pixels) and projected on to an MR head-coil mounted screen using a Canon Xeed SX60 projector system (Canon, UK). Responses were collected using LumitouchTM MRI compatible response boxes (Photon Control Inc, Canada).

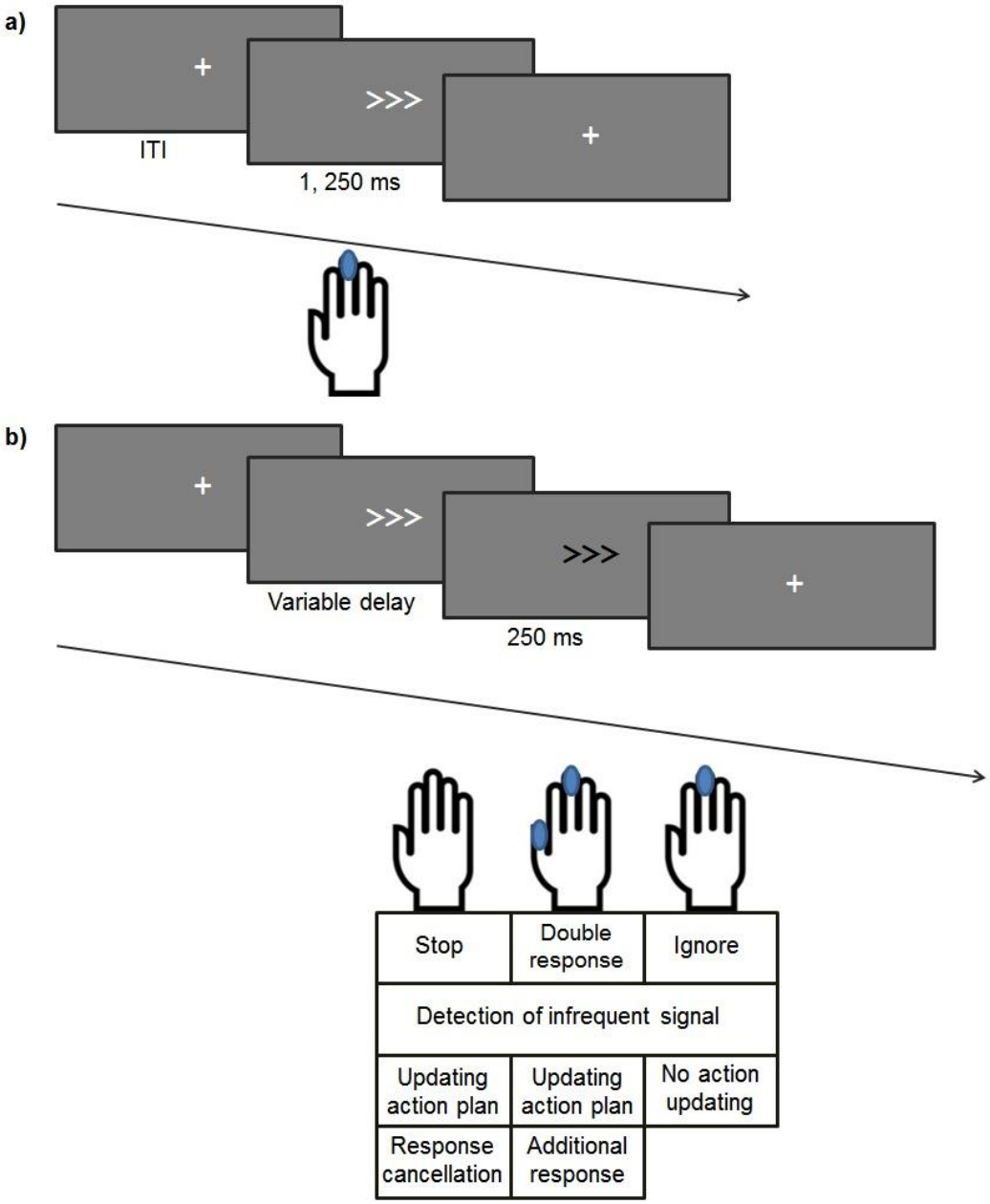

Figure 2.1. Schematic of the context-cueing paradigm employed in the current study (adapted from Verbruggen *et al., 2*010). **(a)** Participants were instructed to respond to the direction of white arrows as fast and as accurately as possible using their right index or right middle finger. **(b)** Signals (the white arrow turning black after a variable delay) were presented on 33% of trials. In the stop context participants were instructed to withhold their response upon presentation of a signal. In the double-response context, they were instructed to execute an additional thumb response; and in the ignore context to only respond to the direction of the arrow (ignoring the presence of the signal). All tasks required participants to detect an infrequent, yet salient, signal. The key difference between the tasks was whether action updating was required, and if so, how the action plans were to be updated upon presentation of a signal. The similarities and differences between the tasks are outlined beneath each task cue. Fixation crosses were presented prior to each trial for the duration of the inter-trial interval (ITI), which was jittered between 500ms, 1,000ms and 2,000ms.

2.2.3. Training session and variable delay

All participants completed a training session prior to testing. As previous work has indicated cognitive control performance to be variable between MRI and lab settings (Assecondi, Vanderperren, Novitskiy *et al*., 2010; Hommel, Fischer, Colzato *et al.*, 2012; Koch, Ruge, Brass *et al.*, 2003; Koten, Langner, Wood, & Willmes, 2013; van Maanen, Forstmann, Keuken *et al.*, 2015), training was completed in a mock MRI scanner designed to mimic the MRI environment. Participants were trained on all tasks separately before receiving mixed training. Witten instructions were provided at the beginning of the session and prior to training on each task (APP10.1.2).

Training on each task was imperative to ensure participants could complete the tasks according to pre-set requirements prior to the testing session. Additionally, the training session provided an opportunity to calibrate the delays to be used in the testing session. To ensure stimuli were consistent across contexts, the SOAs for the IT and DT signal trials were matched to the SSDs in the SST. Each training session began with training on the IT to help participants develop a prepotent tendency to respond to the direction of the arrows. The order of SST and DT training was counterbalanced across participants.

Initial training blocks of each task were comprised of 108 trials (36 signals). Six pre-set stimulus-signal delays (SSDs/SOAs) were used during training (33.3ms, 116.7ms, 200ms, 283.3ms, 366.7ms and 450ms). Delays were based on pilot data of the SST, and included a range of delays where subjects found it relatively easy to stop when the SOA was short (e.g. 33.3ms due to close temporal proximity of arrow stimulus and signal), but more difficult to stop when the SOA was long (e.g. 450ms due to the initiation of the motor response occurring prior to the onset of the stop signal; Figure 2.2). Trial type and signal delays were pseudo-randomised within each block.

Pre-set performance benchmarks were used to ensure participants were able to perform each task in line with instructions. Participants were considered trained once the accuracy and the RT benchmarks outlined in Table 2.1 were met. Additional training criteria for the DT and SST also had to be met and are outlined below.

Table 2.1. Accuracy and reaction time benchmarks for each trial type within the context-cueing paradigm.

	Ignore		Double-response		Stop	
	No-Signal	Signal	No-Signal	Signal	No-Signal	Signal
% correct	85%	85%	85%	85%	85%	>25%, <75%
RT	500ms	500ms	500ms	500ms	600ms	N/A

Note. Accuracy reported as % correct. Both accuracy and reaction time (RT) benchmarks are collapsed across arrow directionality. In the SST, a larger RT benchmark was allocated to account for proactive slowing, a strategy in which participant slow their responses to increase their stop signal success (Verbruggen & Logan, 2009c). Successful inhibition was to occur on 25%-75% of stop signal trials. The RT benchmark for stop signal trials is not applicable as no response is made on successfully inhibited trials.

In the DT, participants were discouraged from 'grouping' their responses to signal trials, a strategy in which participants delay their response to the first task in order to execute two responses as a single grouped action (Pashler, 1994). Inter-response times (i.e. the time between the first and second responses) <50ms was taken as evidence of grouping (e.g. Miller & Ulrich, 2008; Rinkenauer, Ulrich & Wing, 2001). Participants were required to group their responses on no more than 11% of all DT signal trials in each training block (equivalent to 4/36 signal trials).

In the SST, inhibition functions were calculated after each training block using the 6 pre-set SSDs (an initial familiarisation block was excluded). Sigmoid and linear regressions were applied and whichever function best described the data was determined by the quality of fit according to adjusted R^2. This function was then solved to produce the SSD at which successful inhibition occurred on 50% of signal trials (50%SSD). To ensure stability in stopping performance across blocks, the 50%SSD was required to vary by no more than 75ms across successive training blocks.

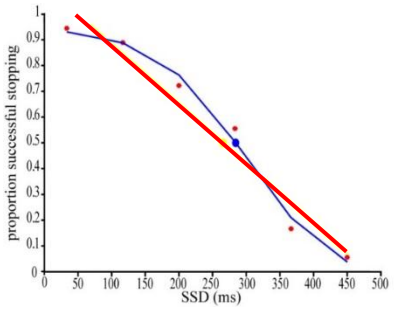

Figure 2.2. Illustration of an individual participant's SST performance over a training session acquired during piloting. Red points correspond to the individual subject's data points and represent the probability of unsuccessful stopping (*p*(respond|signal)) at different stop signal delays (SSDs). The blue regression line is a sigmoidal fit and the red line is the corresponding linear fit. The best fit was used to describe the stopping function and solving for *p*(respond|signal)=.5 to produce the 50%SSD.

Feedback was provided throughout the training session, but limited to prevent the development of response strategies. If performance on any task fell beyond the benchmarks for accuracy (Table 2.1) participants were told to "remember to be as accurate as possible", whereas if mean RTs were exceeded (Table 2.1) then participants were told to "remember to be as fast as possible". During training, feedback was given after every task run and was provided a maximum of 4 times prior to exclusion[30].

Finally, participants received mixed training which included the same behavioural requirements as the subsequent scan session. Participants completed the equivalent of 2 behavioural runs, with each run consisting of 3 blocks of each task (where each block consisted of 18 trials), presented in a randomised order (for block design see Section 2.2.4). The purpose of the mixed training was to ensure that performance was maintained when the tasks were combined. If RTs or accuracy rates fell beyond the benchmarks outlined in Table 2.1 participants received feedback and additional training in the corresponding task(s).

All but 1 participant completed a single training session prior to the testing (1 participant completed 2 sessions). During training, participants completed, on average, 1 run of the IT (*SD*=.4), 1 run of the DT (*SD*=.61), and 4 runs of the SST (*SD*=1.5).

[30] Note, that feedback could be given three times regarding speed and three times regarding accuracy for each trial-type and not trigger the exclusion criteria.

2.2.4. Testing session

Participants who successfully completed the training session proceeded to the scan session. Stimuli were projected onto a screen located ~47cm away from the participant's eyes and viewed through a mirror mounted onto the MR-head coil (located ~12cm away from the participant's eyes). Participants were provided with a full set of task instructions prior to the scan session and brief task instructions prior to each fMRI run (see APP10.1.2).

The testing session included 8 fMRI runs of the behavioural task. Each task block consisted of 18 trials (6 signals) and 3 blocks of each task were presented in each run. 432 trials per context (144 signals) were presented in each testing session. Left and right pointing arrows were randomly presented and occurred with equal probability within each task block. Trial order was constrained so that no more than 3 signal trials were presented successively in any one block to avoid expectation and neuronal habituation effects (Friston, Zarahn, Josephs *et al.*, 1999; Liu, 2004). Task context switched randomly after each block, preventing repeats of the same context and to prevent signal detection issues arising due to scanner drift (i.e. the drift in the BOLD signal due to the slow change in the strength of the static magnetic field over time; Lindquist, 2008). This also helped to ensure the cognitive costs associated with task switching remained relatively equal across task contexts (Rogers & Monsell, 1995). Participants completed a block of each task in a randomised order before commencing the main testing to familiarise themselves with the task; this data was not saved nor analysed.

2.2.4.1. Adjustment of SOAs

The initial SSDs (and therefore SOAs) used in the scan session were calculated using the inhibition functions from the training session. Delay durations were adjusted throughout the scan session (after every 2nd run) to maintain performance on stop signal trials at ~50%. All SOAs in the DT and IT were yoked to SSDs to ensure identical temporal profiles in each context. The % successful stopping performance as a function of SOA was calculated for the two preceding runs and the inhibition function produced indicated the adjustment of the 50%SSD required to maintain performance at 50% in the upcoming two runs. To allow for a range of SSDs/SOAs to be used during

the scan session, the SSDs/SOAs were calculated based on percentiles centred upon the theoretical 50%SSD (8.33%, 25%, 41.67%, 58.33%, 75%, and 91.67%). All derived delays were rounded to the closest screen refresh to ensure timing accuracy. Due to the rounding of SSDs/SOAs to the screen refreshes available, the minimum central SSD used was 108.3ms so that the smallest possible delay was equivalent to one screen refresh (note that although SOAs were set according to percentiles and rounded, 6 separable SOAs were always used)[31]. Feedback was provided after every 2nd run in line with the training session.

2.2.4.2. Physiological Monitoring

Measures relating to physiological monitoring were acquired throughout the scan session as a means to remove associated artefacts commonly found in mid-brain regions, to maximise the power of subsequent analyses, and to improve the signal to noise ratio of the acquired functional data (Bright & Murphy, 2013; Brooks, Faull, Pattinson, & Jenkinson, 2013). All physiological data were continuously acquired during each scan session using a nasal cannula, pulse oximeter and respiration bellows. The nasal cannula was connected to CO_2 and O_2 gas analysers (AEI Technologies, PA, USA). Measures were sampled at 500Hz and logged via a Power1401 (CED, Cambridge, UK) using Spike2.7 (CED, Cambridge, UK). Physiological regressors (cardiac rate, respiration rate, O_2 troughs and end-tidal CO_2) were removed prior to pre-processing (see Section 2.3.2.1). This procedure is detailed in Bright and Murphy (2013) and involves correction for cardiac and respiratory artefacts before variance related to CO_2 and O_2 levels are regressed out of the BOLD data.

[31] Although the initial central SOA to be used in each testing session was calculated based on the best fit acquired during training, later adjustments to this central SSD were driven by participants' performance during the scan session. New inhibition functions were fitted to the data acquired from every second run, and the corresponding fit type acquired from the training session was used to adjust the central SSD for the subsequent behavioural runs. This meant that adjustments were based on either the sigmoid or linear function, which could have been used interchangeably dependent on participant's performance. In addition, adjustments were made to compensate for behavioural changes, where the slope of the fit acquired during training was too steep and the alternative fit was more appropriate based on participant's stopping capacity.

2.2.4.3. fMRI protocol

All scanning was performed in a 3T GE HDx scanner, equipped with an 8-channel head coil. Whole-brain functional images were acquired using an echo planar imaging (EPI) sequence with AC-PC alignment (TR=3000ms, TE= 35ms, matrix size: 64 × 64, flip angle: 90° in-plane resolution: 3.4mm × 3.4mm, 3.4mm slice, no gap). Interleaved slices were acquired in an ascending direction. In total, 156 volumes were acquired over the course of each fMRI run (1248 volumes in total), such that a single fMRI run covered the duration of each of the single behavioural runs. Each run was preceded by the acquisition of 4 dummy scans, to allow for T1-equilibrium (the first task cue was presented during this time).

Once fMRI runs were complete, a field map was acquired to reduce any spatial distortion of the EPI images post-hoc (3D spoiled, gradient-recalled echo sequence, TR=20ms, TE=7ms and 9ms)[32] and a T1-weighted anatomical scan was acquired for each participant (FSPGR, 172 slices[33]; voxel resolution: 1 × 1 × 1mm^3; TR=8ms; TE=3ms, inversion time: 450ms, flip angle of 20°, matrix size: 256 × 256 × 172).

2.3. Analyses

2.3.1. Behavioural analyses

Behavioural analyses were conducted to ensure participants complied with task instructions and for use in establishing the presence of brain-behaviour relationships (Section 2.4.3). Responding to the incorrect direction of the arrow, missed responses and the execution of unnecessary double-responses were considered errors on all no-signal trials. For DT signal trials, failures to execute an additional thumb response or executing a thumb response before executing a response to the arrow stimulus were also considered errors. For stop-signal trials any response was considered an error. Error trials were not excluded from imaging analyses due to the potential for discrepancies in trial numbers (and therefore differential stimuli) across contexts.

[32] After 4 fMRI and behavioural runs were acquired participants were provided the option to have a 5-10 minute comfort break before continuing with the remaining scans. An additional fieldmap (prescription as aforementioned) was acquired prior to this break.

[33] Note that the number of phase encode steps in the slice direction may have been increased to accommodate larger head sizes.

Specific dependent variables (DVs) were computed to explore inhibitory and non-inhibitory action updating. In the DT, DRT2 was calculated as the onset time of the second response minus the onset time of the signal. Additionally, the size and location of the decision bottleneck was quantified. Most previous research of the PRP has used a fixed range of SOAs to quantify the central bottleneck as the rate at which responses are delayed (DRT2) over a range of specific SOAs. This rate or gradient (i.e. the period of time at which the PRP is evident) can then be compared to the DRT2 when SOA is longer or compared to the primary response time (RT1) in isolation (e.g. Broadbent & Gregory, 1967; Hesselmann, Flandin, & Dehaene, 2011). Given the use of multiple, variable SOAs in the current study (as determined by SST performance), a novel dynamic approach to quantifying and locating the bottleneck was adopted. This approach (which was pre-registered) is detailed in Figure 2.3 and was anticipated to adapt to the range of SOAs and individual differences in the expression of the PRP relative to the use of fixed SOAs that are maintained across subjects as per previous work (e.g. Dux *et al., 2*006; Jiang, 2004; Jiang *et al.,* 2004; Ruthruff *et al.,* 2003; Tombu *et al.,* 2011).

Quantifying the size of the bottleneck reveals the overall impact of the PRP on DRT2. The method outlined here was able to adapt to individual RTs, cope with fluctuations in SOAs (owing to adjustments in accord with the SST) and provide a theoretically reliable quantification of the magnitude of slowing caused by the PRP. As such, it was possible for individual's DRT2 performance to be influenced to the same extent, even though the duration of the PRP may differ (i.e. the overall area of the rising linear portion under the fit may be equivalent; Figure 2.3). Previous work has not attempted to quantify the magnitude of the PRP in the same way, rather the focus has been to use fixed SOAs and to assess the contribution of the PRP to subsequent RTs via subtraction between long and short SOAs (see Szameitat *et al.,* 2002)[34].

[34] However, previous work has employed variable SOAs to assess how experimental manipulation may influence the various stages of the decision making process (e.g. via the locus of slack procedure: Pashler, 1994; Pashler & Johnson, 1989; Scweickert, 1978, 1980, 1983; McCann & Johnston, 1992; Miller & Reynolds, 2003), modelled the effects of varying task conditions on PRPs in multi-tasking situations (e.g. Meyer & Kieras, 1997a, 1997b; Wu & Liu, 2003) and modelled the change in PRP as dependent on slopes (Tombu & Jolicoeur, 2011).

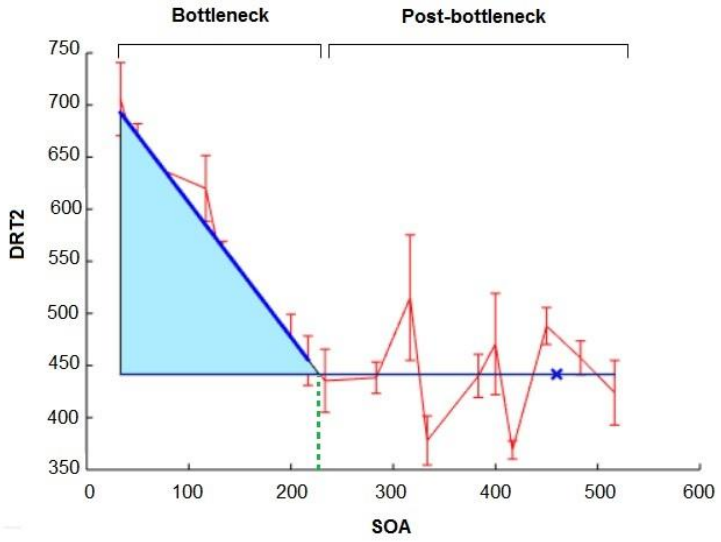

Figure 2.3. Quantification of the size and location of the decision bottleneck in individual subject pilot data. Since the bottleneck represents the 'inability' to select two responses at once (Telford, 1931; Welford, 1952; Pashler, 1994), it was assumed that its influence would not be present after the initial response has been executed on DT signal trials (mean RT1; blue cross). Multiple linear fits were applied to all consecutive DRT2 data points where the SOA was less than mean RT1. Initially, fits were applied to a minimum of three data points, and successive data points were added until the best fit identified. Adjusted R^2 was used to compare fits representative of the bottleneck and the largest value taken as representative of the best fit. The behavioural representation of the PRP can be observed as the elevation in DRT2 across these SOAs (thick blue line). As the frequency of each SOA differed across blocks (due to adjustments in SST performance) fits were weighted according to the inverse of the standard error of each data point. The size of the PRP was then estimated as the area within the rising linear portion of the best fit (light blue area), with the baseline computed as the mean DRT2 across all SOAs that did not contribute the fit (blue horizontal line). Division of within vs. post-bottleneck periods was based on the SOA corresponding to the intercept between the rising linear portion (representative of the PRP) and the baseline (dashed green line).

The division of within- vs. post-bottleneck periods is more consistent with previous work (where short vs. long SOAs have been used; e.g. Dux *et al., 2*006; Jiang, 2004; Jiang *et al.,* 2004; Ruthruff *et al.,* 2003; Tombu *et al.,* 2011) and enabled the exploration of BOLD activity dependent on when DT signals were presented (Section 2.4.3.2). As mentioned, the presentation of signals (either within or post-bottleneck) was hypothesised to have differential effects (Section 2.1.2.2).

Measurement of SSRT in the SST was estimated using the mean and integration methods (Logan & Cowan, 1984)[35]. The mean method is calculated by subtracting the

[35] The mean and integration method were both used to estimate SSRT. The integration method is robust to skewing of no-signal RTs (Verbruggen *et al.*, 2013), and is most often adopted when multiple delays are used (Verbruggen & Logan, 2009). However, the mean method is most often used when fixed delays

SSD at which participants correctly inhibit their responses on 50% trials (here computed using the inhibition functions outlined in Section 2.2.3) from the mean RT on no-signal trials. The integration method involves subtracting the mean SSD from the nth RT; where n is equivalent to the number of no-signal trials in the distribution multiplied by the probability of responding on stop-signal trials. The nth RT is then selected from the no-signal RT distribution when rank ordered (note, all RTs except 0ms RTs were included in the distribution)[36]. For the SST, an additional measure of proactive slowing was computed by subtracting the mean RT for no-signal trials in the IT from the mean RT for no-signal trials in the SST for each participant.

Custom-written Matlab (Mathworks) scripts, SPSS (version 23; Armork, NY: IBM Corp.) and JASP (Version 0.7.1.12, Windows XP; JASP team, 2016)[37] were used to conduct behaviour-based analyses.

2.3.2. fMRI Analysis

2.3.2.1. Pre-processing of fMRI data

Prior to pre-processing, all physiological data were exported into MATLAB and analysed using custom-written scripts designed to remove physiological noise regressors from the EPI data (Bright & Murphy, 2013). Pre-processing and analysis was conducted after their removal using FEAT (version 5.98) in FSL (FMRIB, Oxford, UK; Smith, Jenkinson, Woolrich *et al.*, 2004; Woolrich, Jbabdi *et al.*, 2009). EPI data were motion-corrected using MCFLIRT to account for head movement (Jenkinson *et al.*, *2*002), temporally high-pass filtered at 128s to remove slow drifts in the time series, spatially smoothed using a 5mm full-width-half-maximum Gaussian kernel and pre-whitened to remove temporal autocorrelations in the data (Woolrich *et al.*, *2*001). Field map based correction (B0 unwarping) was also carried out using FSL FUGUE. The resulting images were entered into a general linear model and the following events modelled after convolution with a canonical hemodynamic response function (Glover,

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are employed (Verbruggen *et al.*, *2*013). Although SSDs were adjusted throughout, they were fixed for two runs prior to potential adjustment.

[36] Note SSRT was estimated across all SSDs as opposed to each SSD separately. Therefore the method used here is a variant of the classically applied integration method.

[37] For Bayesian correlation analyses, custom written R code were used (supplied by R. Morey at Cardiff University) to set a JZS prior (as opposed to the Jeffrey's prior offered by JASP).

1999), with temporal derivatives taken into account: Stop Signal, Stop No-Signal, Double Signal, Double No-Signal, Ignore Signal and Ignore No-Signal.

Events were modelled at the onset of each arrow stimulus. To enhance power and to maintain identical stimuli across each condition, all trials were included in the analyses. Cue duration was not explicitly modelled for any analyses and was not used as an implicit baseline measure[38].

2.3.2.1. Whole brain analysis

Whole brain cluster based analyses were conducted[39]. Specific contrasts and disjunctions are presented in Table 2.3. Conjunction analysis is presented in Figure 2.5. The significance threshold was set to Z>2.3, p<0.05 and corrected for multiple comparisons using Gaussian Random Field theory (Friston, Frith, Liddle *et al.*, 1991). Conjunction analysis (Figure 2.5) was based on Z-maps produced via lower level contrasts and formulated as conjunction null hypotheses (Nichols, Brett, Anderson *et al.*, 2005). Disjunction analyses involved the creation of binarised Z-stat masks (using fslmaths) from signal>no-signal contrasts for each task[40]. Group level analyses were conducted with these regions subtracted. Disjunction analyses allow the identification of voxels that are uniquely active (at a pre-defined threshold[41]) under one condition (e.g. stopping an on-going action) and not another (e.g. adding to an on-going response). These analyses differ from conventional contrast approached due to the removal of suprathreshold voxels yielded in one contrast from another. In effect, disjunction analyses remove regions of overlapping activity between contrasts of interest.

[38]Note that ITIs (fixation period) were modelled for exploratory analyses outlined in Chapter 3.

[39] Cluster based analyses were selected based on their apparent ability to increase sensitivity of analyses over voxel based methods and their assumed ability to detect 'real' effects (that is, if you expect a region to be involved in a specific process, you would anticipate that a number of voxels within a region would be co-activated). However, subsequent to thesis submission Ecklund, Nichold & Knuttson (2016) demonstrated that cluster-based statistics do not adequately control for family wise error, and thus there is an increased chance of obtaining false positive results when used. This is due to autocorrelations between activities in neighbouring voxels not conforming to the Gaussian distribution assumed by cluster based approaches. The inflated false positive rate is less so for FSL's FLAME 1 (the analysis package used here) than alternative packages (i.e. it is more conservative), but Ecklund *et al.* recommend the use of voxel-based or permutation-based approaches for fMRI analyses to better control family wise error.

[40] It was assumed that these masks corresponded to activations associated with inhibitory action updating (SST), non-inhibitory action updating (DT) and those associated with infrequent/salient signal detection and motor responding to the arrow stimuli in the absence of updating (IT).

[41] Note, that these analyses were pre-registered prior to data collection to be conducted with exclusion masks thesholded at Z>2.3, p<.05. However, conventional disjunction analyses typically use a lower Z-threshold for the exclusion mask to test for regional specificity.

Conventional contrast approaches only allow inferences regarding the difference in the magnitude of the BOLD activity under different task conditions within a region. All functional imaging data were registered to each subject's own BET stripped anatomical image with a 7 degrees of freedom linear registration and to Montreal Neurological Institute (MNI) standard space using a 12 degrees of freedom linear registration (Smith, 2002; Jenkinson, Pechaud & Smith, 2005).

2.3.2.2. Region of interest analysis

Regions of interest (ROI) were defined *a priori*. The BOLD percent signal change (%BOLD) was extracted using Featquery to establish the presence of brain-behaviour relationships. %BOLD was extracted from contrasts of signal>no-signal within the SST and DT. Left and right ROIs were created for regions previously implicated as crucial to the execution and inhibition of motor responses (see the introduction).

IFG were defined as the combination of the *pars opercularis* and the *pars triangularis* as specified by the Harvard-Oxford cortical atlas (thresholded at 25%). The pre-SMA was defined as the SMA region from the Automated Anatomical Labelling atlas where y>0 (as in Aron & Poldrack, 2006; Tabu *et al.*, 2011; thresholded at 50%). All masks were linearly transformed into MNI space using FLIRT in FSL (Jenkinson & Smith, 2001) prior to thresholding and binarised using fslmaths before interrogation with Featquery.

2.3.3. Data screening

For behavioural and brain-behaviour analyses, conventional null hypothesis testing was undertaken in addition to Bayesian inferential tests capable of summarising the weight of evidence in favour of a difference (H_1) over equality between conditions (H_0) as a Bayes Factor (BF; Dienes, 2011; Dienes, 2014; Rouder *et al.*, 2009; Rouder *et al.*, 2012; Wetzels & Wagenmakers, 2012)[42]. Normality was assessed via Shapiro-Wilk. If this test proved significant (i.e. $p<.05$), then Z-scores were computed for skewness and kurtosis (statistic/standard error) to assess the degree of violation from normality. If Z-scores were >1.96 or < -1.96 then data were either square root or log transformed (indicated

[42] The JZS 'default' prior was used for these analyses (Rouder *et al.*, 2009; Wetzels & Wagenmakers, 2012).

where used; Ghasemi & Zahediasl, 2012; Field, 2013). If negative skewing was demonstrated, data were reflected before transformation (Tabachnick & Fidell, 2007). If non-normality persisted after transformation, non-parametric analyses were conducted. Parametric tests are reported in the main text as Bayesian non-parametric tests are currently under development[43]. Non-parametric analyses (if used) are reported in APP10.1.4 and discrepancies are discussed.

Outliers were identified based on the Median Absolute Difference test (MAD; Leys, Ley, Klein, Bernard, & Licata, 2013, critical value=3; Miller, 1991) for difference tests, while Cook's distance was used for correlational analyses (outliers were identified as Di>4/n; Cook, 1977, 1979). Analyses are reported inclusive of outliers in the main text, but without in APP10.1.4. Discrepancies are discussed. For frequentist analyses, the Holm-Bonferonni method was used to correct for multiple comparisons (Aickin & Gensler, 1996) and the α level for comparison is denoted as the *p*-value subscript (or explicitly within a table) where relevant.

2.4. Results

2.4.1. Behavioural results

Analysis of the behavioural data confirmed that participants were performing in line with pre-specified benchmarks (Figure 2.4a, b and c)**.** In the SST mean RTs to signal trials (i.e. trials on which participants failed to stop their response) were shorter than to no-signal trials ($t_{(29)}$=9.82, $p_{.0167}$<.001, BF=1^{e+8}) in accord with the assumptions of the independent race model (Logan & Cowan, 1984). Conversely, in the IT mean RTs on trials in which signals were presented were longer than those where there was no signal ($t_{(29)}$=7.13, $p_{.025}$<.001, BF=196420.43). Similarly, the execution of the initial response on DT signal trials was longer than that of DT no-signal trials ($t_{(29)}$=3.51, $p_{.05}$<.001, BF=23.6, respectively). No-signal RTs were shortest in the IT and slowest in the SST ($F_{(1.4,40.57)}$=80.64, *p*<.001, BF=1.7^{e+14}, Greenhouse-Geisser corrected; all *p*<.001 and BF>11778 for pairwise comparisons).

In the SST, successful inhibition occurred on ~50% of stop signal trials (*M*=45.53%, *SD*=6.22%) validating the efficacy of the inhibition functions used to set

[43] Based on personal communication with R. Morey (Cardiff University) and E.J. Wagenmakers (University of Amsterdam).

SSDs (adjusted R^2=0.96, *SD*=0.06). SSRTs computed via the mean (*M*=231.71ms, *SD*= 37.55ms) and integration methods (*M*=227.01ms, *SD*= 30.92ms) were in accordance with previous studies that observed comparable SSRT estimates with similar no-signal RTs (here *M*=455.18ms, *SD*=58.40ms; e.g. Verbruggen *et al., 2*010). Although SSRT estimates were longer when estimated using the mean relative to the integration methods (73% of all estimates), this difference was not reliable ($t_{(29)}$=1.63, $p_{.05}$=0.12, BF= 0.63).

In the DT, the locus of the central bottleneck was estimated individually for each participant using the quantification procedure outlined in Section 2.3.1. The mean locus across participants (Figure 2.4d) was identified at an SOA of 195.22ms (*SD*=60.23ms) and the quality of fits were good (adjusted R^2=0.85, *SD*=0.16). As expected, the largest DRT2 was found at the shortest SOA ($F_{(1.36,39.31)}$=122.9, $p_{.05}$<.001, Greenhouse-Geisser corrected, BF=2.23^{e+19}). DRT2 at the shortest SOA was reliably longer than DRT2 at the intercept[44] and DRT2 at the longest SOA, while DRT2 at the longest SOA was also found to be greater than DRT2 at the intercept (all *p*<.001, all BF>60.82). The increase in DRT2 between the intercept and largest SOA was unexpected. Speculatively, this increase in DRT2 may be due to a reduction in preparation to execute an additional response with increased SOA. Greater variability in DRT2 was also found at the longest SOA relative to DRT2 at the shortest or intercept SOA (shortest SOA: *M*=593.53ms, *SD*=70.2ms; intercept SOA: *M*=442.58ms, *SD*=48.99ms; longest SOA: *M*=476.44ms, *SD*=57.64ms).

[44] Where the intercept separates the bottleneck from the post-bottleneck period.

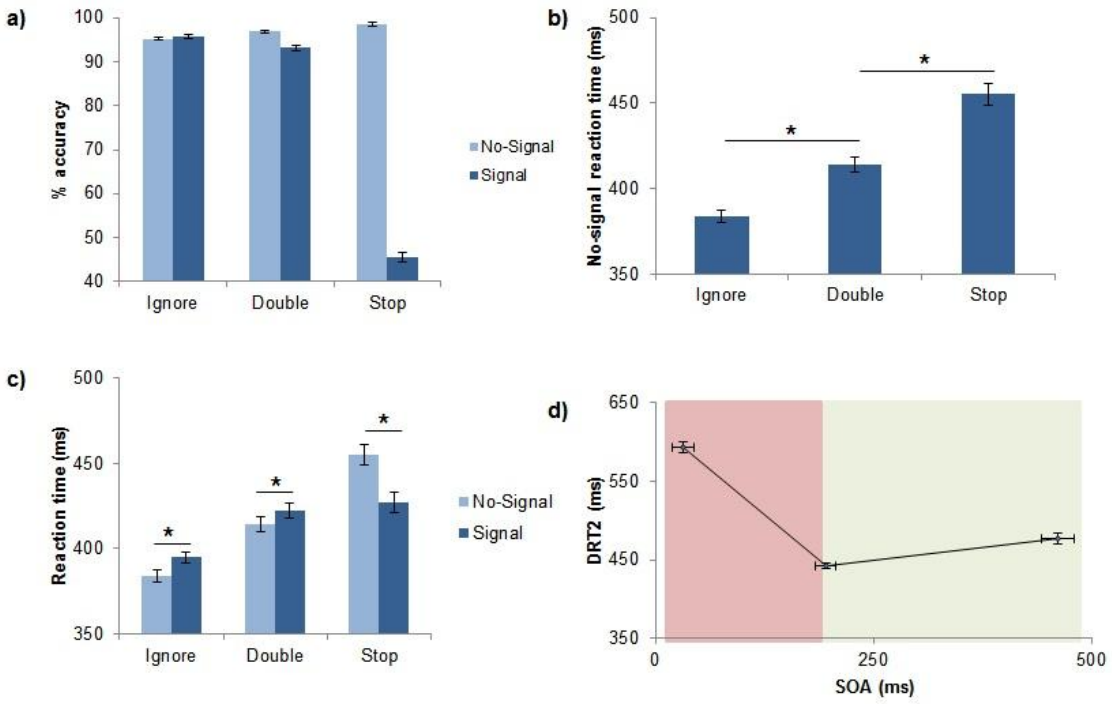


Figure 2.4. Key behavioural results from Study 1. **(a)** % accuracy rates across signal and no-signal trials within each context; **(b)** the significant difference between no-signal trial RTs across tasks; **(c)** the significant difference between signal and no-signal RTs within contexts. Note that in the DT, RTs to signal trials are those of the first response, and in the SST, RTs to signal trials refer to those on failed stops; **(d)** illustrates the mean PRP found across participants. The time to execute the second response relative to the signal onset (DRT2) was found to decrease as the delay between stimulus and signal onsets (SOA) increased during the pre-bottleneck stage (pink area), relative to the post-bottleneck stage (green area). Pre- and post-bottleneck stages were divided according to the point of intercept between weighted linear fits and the mean RT on no-signal trials in the DT (see Section 2.3.1). *****=significant difference according to Holm-Bonferroni adjusted α. Error bars= ±1 within subject standard error (Cousineau, 2005; with correction, Morey, 2008).

2.4.2. Imaging results

The first section of the imaging results describes the findings of the pre-registered[45] analyses aimed at delineating the cortical BOLD response associated with inhibitory and non-inhibitory action updating. These are followed by a set of pre-registered analyses aimed at establishing the presence of brain-behaviour relationships associated with action updating in the SST and DT and the neural correlates of the PRP.

[45] Analyses that were not pre-registered are made explicit in the text.

2.4.2.1. Common and distinct regions recruited under different action updating conditions

The general pattern of observed activity under inhibitory and non-inhibitory action updating conditions were in accord with previous research (Table 2.3), with right frontal dominance associated with response inhibition and bilateral activity associated with double-responding (although left lateralised in motor regions along the precentral and central gyri). These patterns of activity remained consistent when explored in relation to the alternative behavioural contexts and contrasts (see Table 2.3d, f), where greater SST-related activity relative to DT-related activity was yielded in frontal (specifically right) regions. Greater DT-related activity was observed relative to SST-related activity in motor regions. In the IT (Table 2.3c), activity was revealed in occipital, parietal and right frontal regions, in accord with a right lateralised attention network (Corbetta & Shulman, 2002; Corbetta *et al., 2*008).

A central aim of this investigation was to map regional specificity during inhibitory and non-inhibitory action updating conditions, which are most clearly expressed using disjunction analyses. These disjunctions involve removing regions shown to be active under one context from regions shown to be active in another context, both of which have a non-signal baseline. The exclusive response inhibition contrast was (stop signal > stop no-signal) NOT (double signal > double no-signal), and the exclusive non-inhibitory updating contrast was (double signal > double no-signal) NOT (stop signal > stop no-signal)[46]; see Figure 2.5.

Disjunction analyses revealed response inhibition to be uniquely associated with activity in right frontal regions. Specifically, unique activation in the rIFG (39.3% of this region; see also Figure 2.5 and Table 2.2) was largely identified in the anterior rIFG, the *pars triangularis* (69.32% of this region), as opposed to the more posterior, *pars opercularis* (12.72% of this region). Exclusive response inhibition activity in the pre-SMA was relatively small in comparison (14.54% of this region), but connected to a swathe of specific activity encompassing the dorsal ACC, a region previously

[46] The use of ">" refers to conventional contrasts where the resulting BOLD activation patterns correspond to regions of activity that are greater under one condition (>) relative to another. Here, "NOT" refers to the logical not rather than a subtraction. These analyses differ from conventional contrast approaches due to the removal of active supratheshold voxels yielded in one contrast from another. In effect, disjunction analyses remove regions of overlapping activity between contrasts of interest. Note, that these analyses were pre-registered with exclusion masks at Z>2.3, p<.05. However, conventional disjunction analyses typically use a lower Z_threshold for the exclusion mask to test for regional specificity.

implicated in error monitoring (see Botvinick, 2008; Botvinick, Braver, Barch, Carter and Cohen, 2001; Braver, 2005; Botvinick *et al.*, *2*001, 2011). This is not surprising given that the error rates between the SST and DT differ considerably. Unique activity associated with response inhibition was also found in regions commonly activated in response to SST requirements, including the DLPFC (e.g. Erika-Florence *et al.*, 2014; Hughes, Johnston, Fulham, Budd, & Michie, 2013; Sharp *et al.*, *2*010; Chikazoe *et al.*, *2*009).

Under non-inhibitory action updating conditions, both left and right activity was revealed. However, unique activity (as revealed by the disjunction analysis) under non-inhibitory action updating conditions was particularly observed in motor regions along the left precentral and central gyri (Figure 2.5), likely owing to the additional response executed with the right hand on double-signal trials. Exclusivity was evident in posterior voxels of the pre-SMA (16.01% of this region). No voxels in the rIFG were found to be unique to double-responding.

Conjunction analyses (Figure 2.5 and Table 2.2) enabled identification of common regions of activity associated with both inhibitory and non-inhibitory action updating (i.e. overlapping regions of activation). A shared network of activity including occipital, parietal, frontal and subcortical regions was established in accordance with previous work (Chatham et al., 2012; Dodds, Morein-Zamir, & Robbins, 2011; Erika-Florence, Leech, & Hampshire, 2014; Hampshire, 2015; Tabu, Mima, Aso, Takahashi, & Fukuyama, 2011). This commonality was most pronounced in the right hemisphere. In the rIFG, recruitment under general action updating conditions was more pronounced in the posterior *pars opercularis* (87.28% of this region), as opposed to the anterior *pars triangularis* (10.12% of the region; Figure 2.5 and Table 2.2). Together, with the findings from the disjunction analyses, these results indicate rIFG involvement in multiple action updating demands, with the more posterior region associated with general action updating, and the more anterior region associated with the suppression of motor responses.

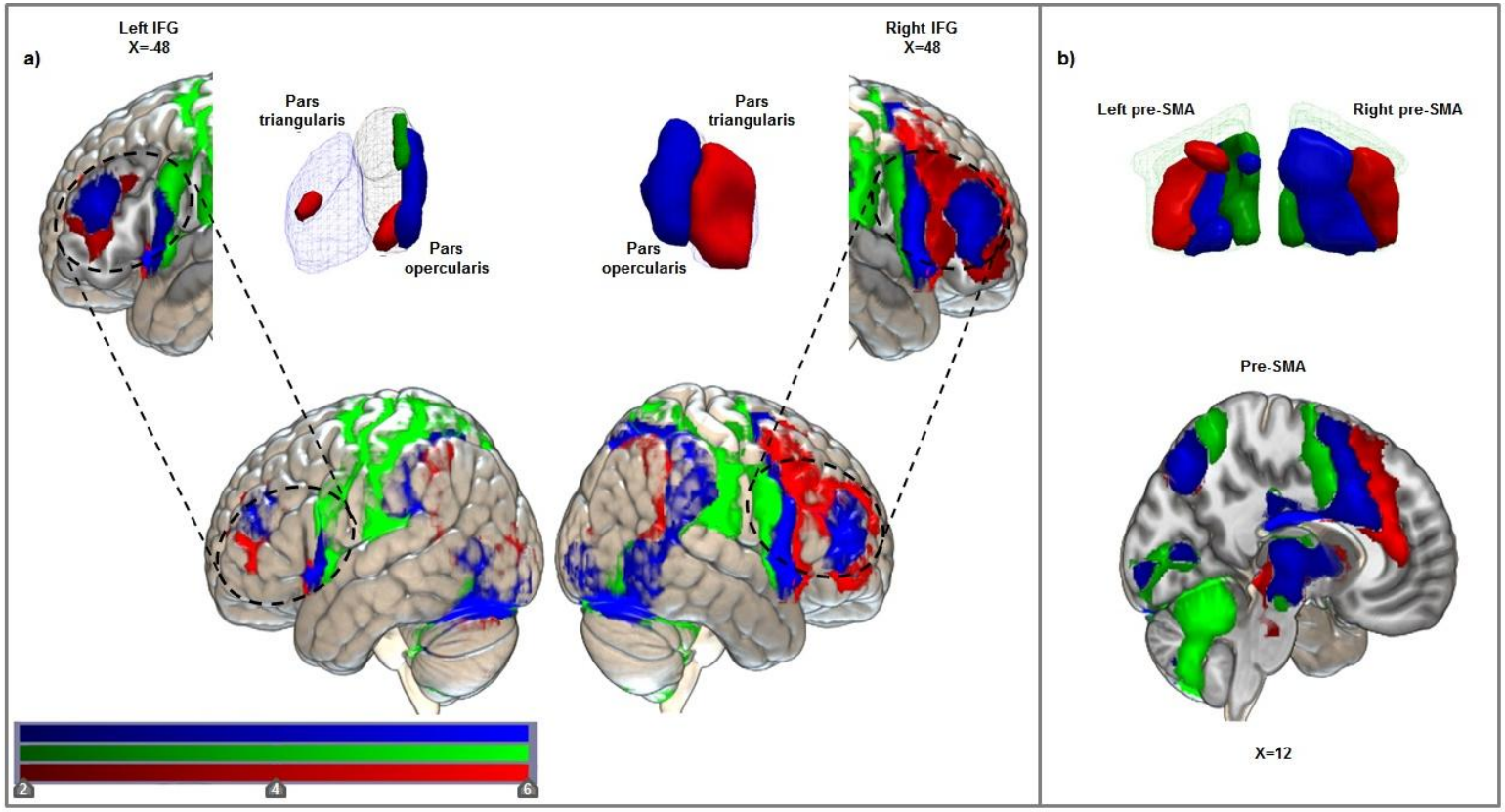


Figure 2.5. Common and distinct regions of activity associated with different forms of action updating. Cluster based activity significant at Z>2.3, p<0.05. Images are illustrated in neurological format (L=L; R=R). Regions unique to inhibitory action updating (stop signal>stop no-signal) after disjunction of voxels activated with non-inhibitory action updating (double signal>double no-signal) are shown in red. Regions specific to double signal>double no-signal after disjunction of voxels activated in the stop signal>stop no-signal contrast are shown in green. Activity common to both inhibitory and non-inhibitory action updating is shown in blue. Panel **(a)** provides a schematic of activity in the right and left IFG and illustrates volume differences under different updating conditions in the *pars opercularis* and *pars triangularis.* Panel **(b)** shows activity in the vicinity of the pre-SMA, and illustrates the volume differences under different updating conditions in the left and right pre-SMA. Scale corresponds to Z-statistic values.

Table 2.2. Summary of the recruitment of cortical ROIs from disjunction and conjunction analyses.

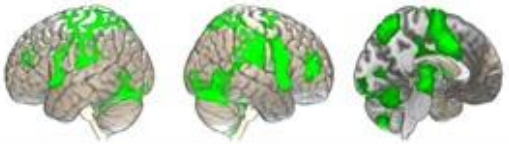
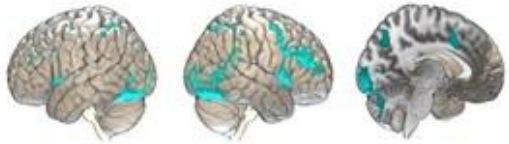
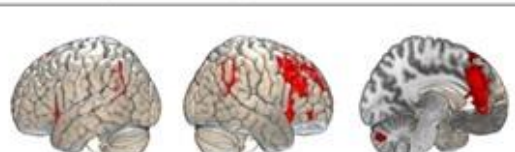
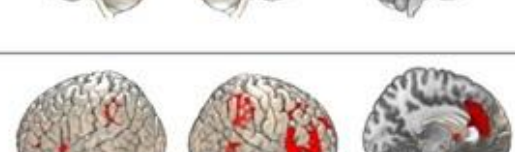
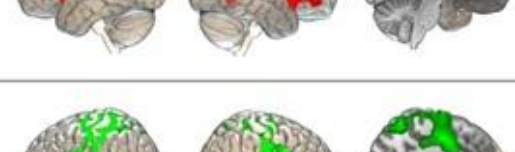
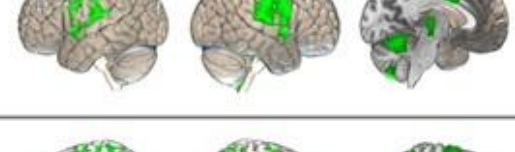
Analysis	ROI	#	%	Z	MNI
(a) Exclusively inhibitory					
Disjunction: (stop signal>stop no-signal) NOT	rIFG	492	39.3	5.64	22,71,51
(double signal>double no-signal)	Pars op	88	12.72	5.64	22,71,51
	Pars tri	348	69.32	5.42	19,80,45
	pre-SMA	347	14.54	6.13	44,73,60
(b) Exclusively non-inhibitory					
Disjunction: (double signal>double no-signal) NOT	rIFG	0	0	0	N/A
(stop signal>stop no-signal)	Pars op	0	0	0	N/A
	Pars tri	0	0	0	N/A
	pre-SMA	381	16.01	6.52	48,66,58
(c) General updating					
Conjunction: (stop signal>stop no-signal) ∩	rIFG	657	52.48	6.17	20,67,47
(double signal>double no-signal)	Pars op	604	87.28	6.17	20,67,47
	Pars tri	51	10.16	3.89	24,79,44
	pre-SMA	722	30.26	5.4	45,71,57
(d) Exclusively inhibitory					
Disjunction: (stop signal>stop no-signal) NOT	rIFG	228	18.21	5.04	20,74,34
(ignore signal>ignore no-signal)	Pars op	69	9.97	4.98	16,71,144
	Pars tri	141	28.08	5.04	20,74,34
	pre-SMA	502	21.04	5.91	42,75,60
(e) Exclusively non-inhibitory					
Disjunction: (double signal>double no-signal) NOT	rIFG	54	4.31	6.88	15,70,46
(ignore signal>ignore no-signal)	Pars op	51	7.37	6.88	15,70,46
	Pars tri	2	0.4	3.01	19,74,33
	pre-SMA	483	20.24	6.47	48,65,59
(f) General updating					
Conjunction: (stop signal> ignore signal) ∩	rIFG	317	25.32	5.3	18,68,41
(double signal>ignore signal)	Pars op	317	45.81	5.3	18,68,41
	Pars tri	0	0	0	N/A
	pre-SMA	492	20.62	4.86	43,67,66

Note. Cluster based activations all exceed Z>2.3, $p<.05$. **ROI**= region of interest; #=number of activated voxels within an ROI; **%**=percent of ROI activated; **Z**=maximum Z value within ROI; **MNI**=MNI coordinates corresponding to maximum Z value; **rIFG**= right inferior frontal gyrus; **Pars op**= right pars opercularis; **Pars tri**= right pars triangularis; **pre-SMA**=pre-supplementary motor area. Here, NOT refers to the logical not rather than a subtraction- that is, the disjunction analyses removes active suprathreshold voxels yielded from one contrast (to the right of the NOT) from another (to the left of the NOT). In effect, disjunction analyses remove regions of overlapping activity between contrasts of interest.

Conversely, the pre-SMA appeared to play a more general role in action updating, with a large portion of this region common to both inhibitory and non-inhibitory action updating (30.26% of this region). As illustrated in Figure 2.5 (see also Table 2.3), the common activity in the pre-SMA was found to extend subcortically towards BG regions thought to support both the execution and inhibition of responses (Albin *et al.*, 1989; Alexander & Crutcher, 1990; Nambu *et al., 2*002). The common activity in the pre-SMA was found to be located centrally (with a slight right bias) in this structure. As revealed by the disjunction analyses (Figure 2.5), cancelling a response was associated with an anterior spread of activity towards the dorsal ACC, while double-responding was associated with posterior activity in the SMA - a region known to underlie the control of movement (Solodkin, Hlustik, Noll, & Small, 2001).

Activity corresponding to signal detection in the IT was taken into account through additional contrast analyses (Table 2.3, c, e, g). Similar results were obtained for inhibitory and non-inhibitory action updating when either stop signal>stop no-signal or double signal >double no-signal were contrasted against ignore signal>ignore no-signal.

Table 2.3. Significant BOLD activity yielded from pre-registered contrasts.

Contrast and aim	Whole brain activity	Location	# voxels	Max. Z	Coords
a) Stop Signal > Stop No-Signal To establish regions of activity associated with inhibitory action updating relative to execution of a response.		R lateral occipital cortex	25755	7.79	34, -60, 48
		R insular cortex	23523	7.14	36, 20, -8
		L insular cortex	6279	7.31	-34, 18, 2
b) Double Signal > Double No-Signal To establish regions of activity associated with non-inhibitory action updating relative to execution of a response.		L precentral gyrus	80268	8.86	-48, -28, 52
c) Ignore Signal > Ignore No-Signal To establish regions of activity associated with processing an irrelevant signal and execution of a response relative to execution of a response		L occipital pole	25350	7.03	-28, -92, -8
		R precentral gyrus	13736	5.89	50, 8, 28
		L posterior cingulate gyrus	845	4.48	-4, -32, 22
d) (Stop Signal> Stop No-Signal) > (Double Signal>Double No-Signal) To establish regions of activity associated with inhibitory action updating relative to non-inhibitory action updating and the execution of a response		R paracingulate gyrus	13033	5.84	4, 36, 30
		R angular gyrus	2291	4.75	50, -50, 38
		L frontal orbital cortex	979	5.00	-38, 16, -14
		L angular gyrus	970	5.14	-58, -54, 34
		L cerebellum	810	4.00	-16, -82, -36
e) (Stop Signal > Stop No-Signal) > (Ignore Signal > Ignore No-Signal) To establish regions of activity associated with inhibitory action updating relative to processing an irrelevant stimulus and execution of a response		R insular cortex	1191	6.2	38, 16, -10
		R supramarginal gyrus	3905	5.12	62, -42, 32
		L insular cortex	1418	6.13	-36, 16, -12
		L supramarginal gyrus	1190	5.1	-58, -42, 36
		L frontal pole	1005	3.89	-26, 48, 30
f) (Double Signal > Double No-Signal) > (Stop Signal > Stop No-Signal) To establish regions of activity associated with non-inhibitory action updating relative to inhibitory action updating and the execution of a response		L cerebellum	972	3.98	-32, -62, -38
		L postcentral gyrus	34944	8.58	-56, -22, 48
		R cerebellum	9532	7.12	14, -54, -26
g) (Double Signal > Double No-Signal) > (Ignore Signal > Ignore No-Signal) To establish regions of activity associated with non-inhibitory action updating relative to processing an irrelevant stimulus and execution of a response		L postcentral gyrus	43324	8.1	-54, -26, 48

Note. Cluster based activity significant at Z>2.3, p<0.05.The aim and rational behind each of the contrasts is outlined. Images are illustrated in neurological format (L=L; R=R). Details regarding significant regions of activity are reported. **Location**= region of peak activity as indicated using the Harvard-Oxford cortical atlas; **L**=left; **R**= right; **# voxels**= number of voxels within significant clusters; **Max Z**= maximum Z-value within specified cluster; **Coords**= coordinates of maximum Z-value presented as X, Y, Z co-ordinates in 2mm MNI space. Red regions of activity represent that associated with inhibitory action updating, green regions represent activity associated with non-inhibitory action updating, light blue regions represent associated with signal detection (with no action updating) in the IT. Here, > refers to conventional contrast analyses that result in BOLD activation patterns that correspond to regions of activity that are greater in one condition (>) relative to another. In effect, contrast analyses reveal the difference in magnitude of activity between conditons.

2.4.2.2. Differential recruitment of the rIFG and pre-SMA

As substantial pre-SMA and rIFG activity was observed under all action updating conditions (Table 2.3), the extent of differential recruitment was quantitatively explored. These analyses were not pre-registered. The mean %BOLD from within masks representative of each ROI was drawn from signal>no-signal contrasts computed for each context. One-sample t-tests and Bayesian equivalents revealed significant %BOLD in the rIFG for each context (SST: $t_{(29)}$=7.63, $p_{.017}$<.001, BF= 2.38^{e+11}, DT: $t_{(29)}$=5.79, $p_{0.05}$<.001, BF= 6665, IT: $t_{(29)}$=6.92, $p_{.025}$<.001, BF=116375.07). Significant activity associated with inhibitory and non-inhibitory updating requirements was also established in the pre-SMA (SST: $t_{(29)}$=4.64, $p_{.017}$<.001, BF= 359.98, DT: $t_{(29)}$=3.02, $p_{.025}$=.01, BF=7.89). However, the presence of the signal in the IT was not associated with a significant increase in %BOLD in the pre-SMA ($t_{(29)}$=1.01, $p_{.05}$=.323, BF=0.31). This suggests that the detection of a signal in the IT was not sufficient to increase pre-SMA activity and may indicate this region is not crucial to conditions where action plans do not require adjustment.

Differences in the extent to which each region was recruited under the different task contexts was investigated with repeated measures ANOVA, applied to the %BOLD associated with the signal>no-signal contrast in each context (Figure 2.6). A main effect of ROI revaled the rIFG to be recruited to a greater extent than the pre-SMA ($F_{(1,29)}$=12.6, p<.001, BF=9.94). A main effect of task was also found ($F_{(2,58)}$=8.08, p<.001, BF=958.44), whereby the SST was found to be associated with significantly greater activity than the IT ($p_{.0167}$<.001, BF=45.58). No other differences between the tasks were found (SST vs. DT: $p_{.025}$=.043, BF=1.36; DT vs. IT: p=.052, BF=1.16). No interaction between ROI and task was identified ($F_{(2,58)}$=2.92, p=.06, BF=0.43). Thus, the differential recruitment of each ROI was not task-dependent (see Figure 2.6a). However, subsequent to outlier exclusion an interaction effect was found ($F_{(2,52)}$=3.74, p=.031), although the corresponding BF was inconclusive (BF=0.62). This possible interaction appeared to be associated with differences in rIFG recruitment between tasks, with greater activity found under SST relative to DT ($p_{.025}$=.002, BF=20.13) and IT ($p_{.0167}$<.001, BF=74.6) conditions. However, no difference was found between activity under DT and IT conditions (p=.342, BF=0.31). No significant differences were found in pre-SMA recruitment under different task conditions (see APP10.4.1.2).

Given this result and the differences in uniquely activated voxels within the anterior and posterior rIFG under different response control conditions identified above, an additional repeated measures ANOVA was conducted. Here, I aimed to establish whether there were differences in the recruitment of the *pars opercularis* and *pars triangularis* under different response control conditions[47]. A main effect of ROI revealed ($F_{(1,29)}$=58.84, p<.001, BF=159555.14) greater recruitment of the *pars opercularis* relative to the *pars triangularis*. A main effect of task ($F_{(2,58)}$=9.89, p<.001, BF=6707.87) also revealed the SST to be associated with significantly greater activity than the DT ($p_{.025}$=.001, BF=28.48) and the IT ($p_{.0167}$=.001, BF=27.06), although no difference was found between the DT and IT (p=.543, BF=0.23). Main effects were qualified by an interaction between ROI and task ($F_{(2,58)}$=12.39, p<.001, BF=4.02 see Figure 2.6b[48]). Pair-wise comparisons revealed difference in recruitment of the *pars opercualris* and *pars triangularis* under different response control conditions (Figure 2.7). In the *pars opercularis*, significantly greater activity was found to be associated with the SST relative to the DT and IT, and greater activity in the DT relative to the IT (all p<.024, all BFs>2.14). This graded pattern of activity (Figure 2.7a) suggests the *pars opercularis* may be differentially recruited depending on the necessary updating requirements. Similarly, activity in the *pars triangularis* was found to be greater under SST relative to DT ($p_{.017}$<.001, BF= 68.35; Figure 2.7b) and no updating in the IT (SST vs. IT: $p_{.025}$=.023, BF= 2.26), but did not differ upon presentation of the infrequent signal in the DT relative the IT (DT vs. IT: p=.104, BF= 0.68).

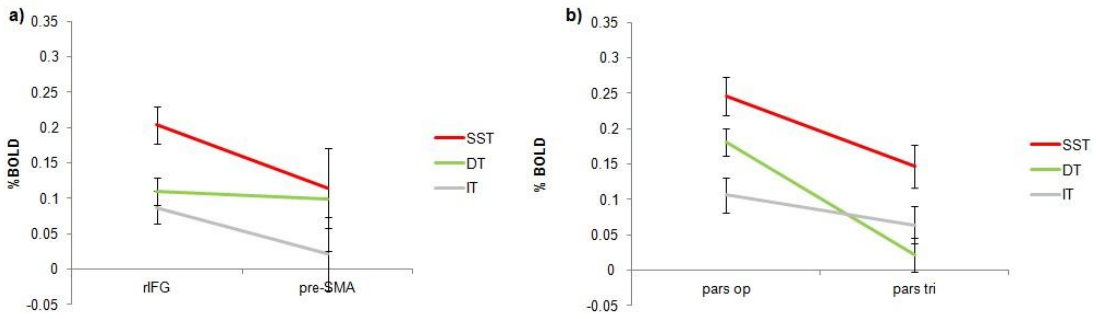


Figure 2.6. %BOLD drawn from **(a)** the pre-SMA and rIFG **(b)** the *pars opercularis and pars triangularis* from the signal>no-signal contrasts in the SST (red), DT (green) and IT (grey). *=significance after Holm-Bonferroni adjusted α. Error bars= ±1 within subject standard error (Cousineau, 2005; with correction, Morey, 2008).

[47] This analysis was conducted after the data were transformed.

[48] Note that the BF associated with the interaction was reduced to <3 after outlier removal (BF=2.28; see APP10.1.4.1.2)

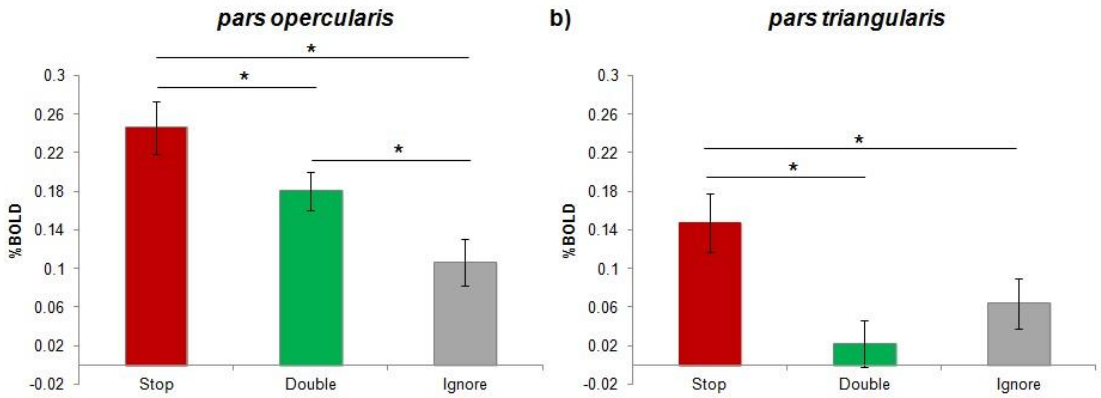


Figure 2.7: %BOLD drawn from the subdividions of the rIFG from the signal>no-signal contrasts in the SST (red), DT (green) and IT (grey). Differences between %BOLD for each context are shown for the **(a)** the *pars opercularis* and **(b)** the *pars triangularis*. *=significance after Holm-Bonferroni adjusted α. Error bars= ±1 within subject standard error (Cousineau, 2005; with correction, Morey, 2008).

Collectively, the ROI analyses indicate the rIFG, as a whole and its sub-regions, to be recruited to a greater extent under SST relative to DT and IT conditions. This, in combination with the anterior spread of activity associated with response inhibition (disjunction analyses performed above), indicate the anterior rIFG (particularly the *pars triangularis*) may be specialised for response inhibition, relative to when action plans require addition to or are run to completion. However, it is important to note that complete specialisation requires further exploration. The rIFG as a whole, and its subdivdisions, were found to be recruited to a greater degree upon signal presentation vs. go stimuli across all tasks.Even though the %BOLD change was of a lesser extent in the DT and the IT relative to the SST, small changes does not simply indicate these regions are not involved (Van Horn & Poldrack, 2009; see also de Hollander, Wagenmakers, Waldrop & Forstmann, 2014).

2.4.3. Brain-behaviour relationships

To further explore the functional specialisation of the IFG and the pre-SMA, additional analyses were conducted[49] (analyses of subcortical ROIs are reported in Chapter 3). These analyses were conducted to establish whether %BOLD in any of the ROIs was

[49] Analysis of the IFG and pre-SMA were pre-registered, but analysis of the *pars opercularis* and *pars triangularis* were not. These analyses were conducted due to the distinction in activation revealed between contexts (Section 2.4.2.2. and Figure 2.6).

related to behavioural indices of action updating. %BOLD was extracted from contrasts thought to best reflect inhibitory and non-inhibitory action updating: stop signal>stop no-signal and double-signal>double no-signal, respectively. Initial analyses were aimed at exploring the correlational relationships between SSRT and DRT2 and %BOLD. Further analyses were conducted subsequent to median split of behavioural indices of action updating using independent sample t-tests. These were run due to the presence of non-normal (slightly bimodal) distributions[50] (see Figure 2.8). Additional analyses were conducted to establish whether correlational relationships were present between %BOLD and proactive slowing in the SST, and size of the decision bottleneck in the DT. Finally analyses were conducted to establish whether the demands related to each of the tasks modulated activity in ROIs. These analyses aimed at exploring the %BOLD in relation to the SSD in the SST and SOA in the DT. 6 delays (SSDs/SOAs) were used for each behavioural run. As within-subject data were highly correlated, separate analyses were conducted for each participant and each ROI separately. Resultant coefficients were then subjected to either Frequentist or Bayesian one-sample t-tests to ascertain whether there was an effect of increasing delay between stimulus and signal and %BOLD. Differences in %BOLD in each ROI was also explored at short vs. long delays- in the SST, SSDs were divided according to the 50%SSD established via the inhibition functions (Section 2.2.3) and in the DT, SOAs were divided according to the intercept separating the within- and post-bottleneck phases established using the quantification procedure (Section 2.3.1). Analysis of the size of the bottleneck and within- vs. post-bottleneck periods were expected to reveal the neural correlates of the PRP. Results are reported separately for inhibitory and non-inhibitory action updating analyses.

[50] The analysis of data subsequent to median split were not pre-registered and were driven by the observation of the non-normal distributions in behavioural indices of action updating (Figure 2.8).

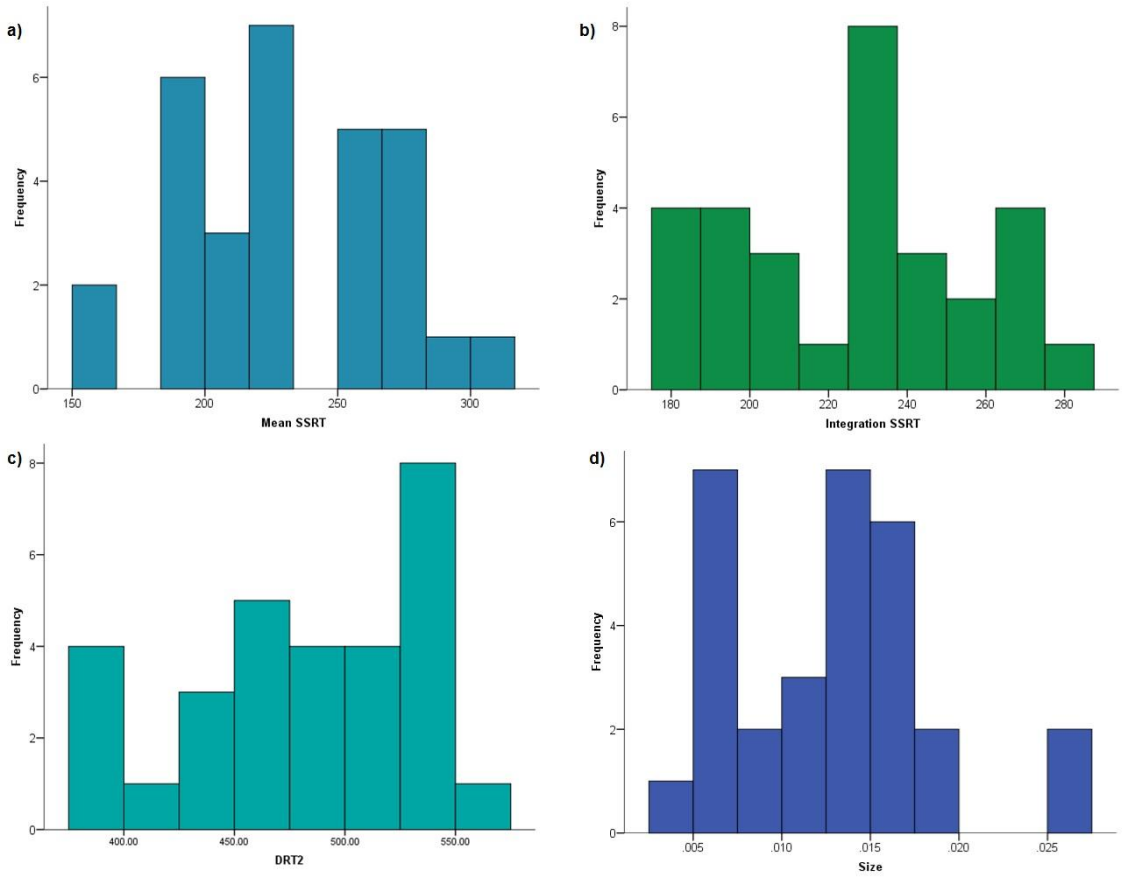


Figure 2.8. Histograms illustrating the distribution of stop signal reaction times (SSRTs) when estimated using **(a)** the mean method and **(b)** integration methods, **(c)** the latency of the double-response process (DRT2), and **(d)** the estimated size of the PRP. The plots indicate the presence of non-normal distributions, particularly for the SSRT estimates.

2.4.3.1. Relationships between indices of inhibitory action updating and %BOLD

SSRT provides an index of individual inhibitory ability, with short SSRTs illustrating more efficient inhibition than longer SSRTs (Logan & Cowan, 1984). It was anticipated that a negative correlation between SSRT and %BOLD would be found in regions crucial for response inhibition, as per previous work (e.g. Aron *et al.,* 2007; Aron & Poldrack, 2006). Contrary to this hypothesis, analyses reveal evidence of no relationships (Table 2.4) with all BFs close to or in favour of the null (i.e. BF<1/3). It is unlikely that the lack of effects were the result of participants adopting slowing strategies as no correlations between %BOLD and proactive slowing[51] were found (Table 2.4). As SSRT distributions appeared non-normal (Figure 2.8a, b) data were re-

[51] For clarity, the measure of proactive slowing was computed as the difference between no-signal RTs in the SST and in the IT.

analysed subsequent to median split of SSRT. Independent t-tests of %BOLD at short vs. long SSRT proved inconclusive (Table 2.5).

Table 2.4. Correlations between %BOLD in cortical ROIs acquired from the contrast stop signal>stop no-signal with SSRT and proactive slowing.

	Mean SSRT			Integration SSRT			Proactive Slowing^{+}		
ROI	r	*p*	BF	r	*p*	BF	r	*p*	BF
R IFG	0.2	.294	0.33	0.23	.221	0.39	-0.23	.227	0.39
R preSMA	0.18	.331	0.3	0.18	.349	0.3	0.11	.548	0.23
L IFG	0.01	.968	0.19	0.02	.924	0.2	0.12	.528	0.23
L preSMA	0.19	.307	0.31	0.23	.216	0.39	0.15	.441	0.26
R pars op	0.22	.236	0.37	0.23	.223	0.39	-0.33	.079	0.87
R pars tri	0.16	.412	0.27	0.21	.274	0.35	-0.08	.684	0.21

Note. Stop signal reaction time (**SSRT**) was estimated using the mean and integration methods, separately. **ROI**=region of interest; **r=**Pearson's correlation coefficient; ***p***= *p*-value; **BF**=Bayes Factor; **R**=right; **L**=left; **IFG**=inferior frontal gyrus; **preSMA**=pre-supplementary motor area**; pars op**= pars opercularis; **pars tri**= pars triangularis; $^{+}$= computed on transformed data. α-level not shown as all *p*>.05. All degrees of freedom=28.

Table 2.5. Differences in %BOLD in cortical ROIs between participants with short vs. long SSRTs. Independent t-tests were conducted subsequent to median split of SSRT.

	Mean SSRT			Integration SSRT		
ROI	t	*p*	BF	t	*p*	BF
R IFG	-1.34	.191	0.69	-1.36	.186	0.69
R preSMA	-0.7	.493	0.42	-1.07	.294	0.53
L IFG$^{++◊◊}$	-0.67	.51	0.42	-0.49	.625	0.38
L preSMA	-0.58	.567	0.4	-0.69	.497	0.41
R pars op$^{◊}$	-1.4	.173	0.73	-1.42	.167	0.73
R pars tri	-1.23	.229	0.62	-1.18	.249	0.58

Note. Stop signal reaction time (**SSRT**) was estimated using the mean and integration methods, separately. **ROI**=region of interest; **t=**t-value; ***p***=p-value; **BF**=Bayes Factor; **R**=right; **L**=left; **IFG**=inferior frontal gyrus; **preSMA**=pre-supplementary motor area**; pars op**= pars opercularis; **pars tri**= pars triangularis; $^{◊}$= conducted on transformed data when SSRT estimated using the integration method; $^{++}$ and $^{◊◊}$=non-parametric analysis required when SSRT was estimated using the mean and integration methods, respectively. 2 participants SSRT were equal to the median value when estimated using the mean method and were excluded from the analyses. Degrees of freedom= 26 for analysis using the mean method, and 28 for analysis using the integration method. α-level not shown as all *p*>.05.

It is well established that increasing the duration between stimulus and signal presentation in the SST decreases the probability of successful inhibition (Logan & Cowan, 1984). Therefore, I anticipated differences in activity in those ROIs crucial to response inhibition as a function of SSD. Evidence for a relationship between %BOLD and SSD was found in bilateral pre-SMA (Table 2.6, Figure 2.9a): these regions were recruited to a greater extent as SSD increased. Similarly, activity was also found to be greater in right pre-SMA when signals were presented after the 50%SSD (i.e. long SSDs where there was a low probability of stop signal success) relative to when signals were presented prior to the 50%SSD (i.e. short SSDs where there was a high probability of stop signal success; Table 2.6, Figure 2.9b). Outlier exclusion (Table APP10.1.3) also indicated evidence for greater recruitment of the *pars opercularis* when signals where presented after (post) relative to before (pre) 50%SSD (BF=2.97). Although response execution is more likely at longer SSDs relative to short SSDs, contrasting signal trials against no-signal trials (where responses were to be made) makes this an unlikely explanation. Rather the low probability of stop signal success at long SSDs is likely to result in increased effort to cancel an action or increased attentional processes associated with error and performance monitoring when stop signal success is limited.

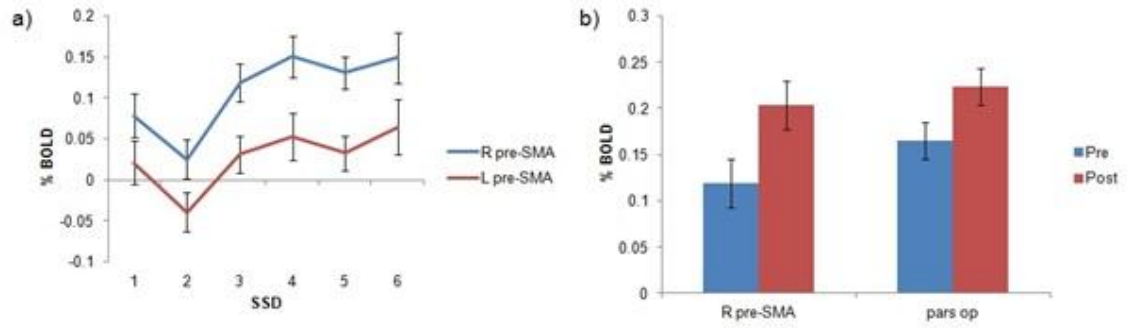


Figure 2.9. Change in %BOLD with SSD. **(a)** %BOLD in left (L) and right (R) pre-SMA with increasing SSD (where 1 is the shortest SSD and 6 is the longest); **(b)** %BOLD in the R pre-SMA and R *pars opercularis* (pars op; after outlier exclusion, see Table APP10.1.3) when stop signals were presented before or after the 50%SSD. Corresponding *p*-values did not survive correction for multiple comparisons, but all BFs>3. Error bars= ±1 within subject standard error (Cousineau, 2005; with correction, Morey, 2008).

Table 2.6. One-sample t-tests of coefficients yielded from within-subject correlations across SSD and paired sample t-tests between %BOLD when stop signals were presented before or after the 50%SSD.

	Correlation SSD^{++}				Pre vs. post 50%SSD			
ROI	t	*p*	α	BF	t	*p*	α	BF
R IFG	1.28	.209		0.41	-1.07	.292		0.33
R preSMA	3.26	.003	0.0028	**13.22**	-3.26	.003	0.0028	**13.26**
L IFG	0.08	.94		0.2	0.35	.732		0.21
L preSMA	3	.006		**7.42**	-1.96	.06		1.03
R pars op	2.1	.045		1.31	-1.97	.059		1.05
R pars tri	-0.21	.833		0.2	0.31	.756		0.2

Note. **Correlation SSD**: as within-subject %BOLD across SSDs were highly correlated, separate correlations were conducted for each participant and each ROI. Resultant Pearson's coefficients were subjected to either Frequentist or Bayesian one-sample t-tests to ascertain whether there was an effect of increasing delay between stimulus and signal; **Pre- vs. post 50%SSD** refers to the results of paired sample t-tests when signals were presented before or after the 50%SSD; **ROI**=region of interest; **t=**t-value; ***p***=p-value; **α**= alpha-level; **BF**=Bayes Factor, BFs>3 reported in bold; **R**=right; **L**=left; **IFG**=inferior frontal gyrus; **preSMA**=pre-supplementary motor area**; pars op**= pars opercularis; **pars tri**= pars triangularis. All degrees of freedom=29. Note that Holm-Bonferonni correction was conducted across all ROIs including subcortical ROIs reported in Chapter 3 (Section 3.2.1.1). α calculated as: $\alpha(k)=0.05/(n-k+1)$, where *n* is the number of ROIs (in this case 18), and *k* is the rank ordering of *p*-values from 1 to *n.* $^{++}$=non-parametric correlations conducted separately and subjected to one-sample t-tests (see APP10.1.4.2.1.3).

2.4.3.2. Relationships between indices of non-inhibitory action updating and %BOLD

As mentioned, the elongation of DRT2 at short SOAs may be representative of either a structural or strategic bottleneck (Telford, 1931; Welford, 1952; Pashler, 1994). Consequently, it was predicted that regions that may provide a limitation or are crucial for response selection and the execution of response sequences, would exhibit greater recruitment at short vs. long SOAs as per previous work (e.g. Herath, Klingberg, Young, *et al., 2*001; Jiang, 2004; Dux *et al., 2*006; Szameitat *et al., 2*002; although no difference was found by Jiang, Saxe, & Kanwisher, 2004). Furthermore, participants with longer DRT2 were hypothesised to be less efficient at non-inhibitory action updating than those with shorter DRT2s, due to a greater PRP influence. As such, positive correlations were anticipated between DRT2 and %BOLD within regions crucial to non-inhibitory action updating. It was also anticipated that the size of the PRP (as computed via the quantification procedure outlined in Section 2.3.1) would be correlated with activity in regions crucial to non-inhibitory processes; in particular,

larger estimates of size (thought to be representative of greater PRPs) were anticipated to be associated with greater activation. However, no relationships were found (Table 2.7), and evidence largely favoured the null. Therefore these ROIs may not host mechanisms that impose structural limitations on decision-making processes in the DT. This was supported by the lack of effects observed when analysis were conducted subsequent to median split of the data (due to the non-normal distribution of both DRT2 and estimated size of the PRP; Figure 2.8c, d). Evidence of %BOLD differences in ROIs for participants with short vs. long DRT2 and large vs. small PRPs proved largely inconclusive, but were in favour of the null (Table 2.8).

Table 2.7. Correlations between %BOLD in cortical ROIs acquired from the contrast double signal>double no-signal with DRT2 and estimated size of the PRP.

	DRT2			Size		
ROI	r	*p*	BF	r	*p*	BF
R IFG	-0.07	.735	0.21	0.24	.206	0.42
R preSMA	-0.16	.405	0.27	0.3	.105	0.66
L IFG	-0.14	.473	0.25	0.19	.317	0.31
L preSMA	-0.27	.15	0.52	0.11	.565	0.23

Note. **DRT2**=the latency of the non-inhibitory action updating process; **Size**=size of the PRP; **ROI**= region of interest, **r=** Pearson's correlation coefficient; ***p***=p-value; **BF**=Bayes Factor; **R**=right; **L**=left; **IFG**=inferior frontal gyrus; **preSMA**=pre-supplementary motor area**.** α not shown as all *p*>.05. All degrees of freedom=28.

Table 2.8. Differences in %BOLD in cortical ROIs between participants with short vs. long DRT2 and small vs. large PRPs. Independent t-tests were conducted subsequent to median split of DRT2 and size of the PRP.

	DRT2				Size			
ROI	t	df	*p*	BF	t	df	*p*	BF
R IFG	1.59	24.23	.124	0.88	-1.23	25	.229	063
R preSMA	1.79	28	.085	1.12	-0.43	25	.671	0.92
L IFG	0.6	28	.555	0.39	-1.61	25	.119	0.38
L preSMA	1.49	28	.147	0.79	-0.44	25	.661	0.39

Note. **DRT2**=the latency of the non-inhibitory action updating process; **Size**=size of the PRP; **ROI**= region of interest, **t=** t-value; **df**= degrees of freedom (adjusted where Levene's test for homoscedasticity was significant); ***p***=p-value; **BF**=Bayes Factor; **R**=right; **L**=left; **IFG**=inferior frontal gyrus; **preSMA**=pre-supplementary motor area**.** α not shown as all *p*>.05. Note that 3 subjects size of the bottleneck were identical to the median value and were thus excluded from this analysis.

In the DT, whether signals were presented within or after the bottleneck period was dependent on the SOA. Here, it was anticipated that increased SOA would be associated with decreased %BOLD due to the reduction in bottleneck limitations in the post- relative to the within-bottleneck period, and that %BOLD associated with short SOAs be greater than long SOAs when separated into within and post-bottleneck periods, respectively. Results are summarised in Table 2.9.

BFs indicated evidence for a relationship between %BOLD and SOA in bilateral pre-SMA. Elevated %BOLD in these ROIs was observed with increasing SOA (Figure 2.10a). Contrary to expectations it appeared that activity generally increased with SOA. Consistent with this, DRT2 were found to decrease within the bottleneck phase, but subsequently increase once this had passed (Figure 2.4d). Similar decrease and increased %BOLD were observed in the pre-SMA during the within and post-bottleneck phases, respectively (Figure 2.10b). As errors were infrequent in the DT (Figure 2.4a) it is unlikely that this response is associated with post-error monitoring. However, increased pre-SMA activity may be expressed when detecting and responding to a signal is unexpected and preparation to update responses is low.

Table 2.9. One-sample t-tests of coefficients yielded from within-subject correlations across SOAs and paired sample t-tests between %BOLD when double signals were presented within or post decision bottleneck.

	Correlation SOA^{++}				Pre vs. post			
ROI	t	*p*	α	BF	t	*p*	α	BF
R IFG^{++}	1.33	.195		0.43	-1.86	.073		0.88
R preSMA	2.76	.010		**4.51**	-3.19	.003	0.0031	**11.34**
L IFG^{++}	-1.35	.186		0.44	-0.54	.595		0.22
L preSMA^{++}	2.75	.010	.0031	**4.46**	-3.13	.004		**9.84**

Note. **Correlation SOA**: as within-subject %BOLD across SOAs were highly correlated, separate correlations were conducted for each participant and each ROI. Resultant Pearson's coefficients were subjected to either Frequentist or Bayesian one-sample t-tests to ascertain whether there was an effect of increasing delay between stimulus and signal. **Pre- vs. post** refers to the results of paired sample t-tests when signals were presented within or post-bottleneck. **ROI**=region of interest; **t=**t-value; ***p***=p-value; **α**= alpha-level; **BF**=Bayes Factor, BFs>3 reported in bold; **R**=right; **L**=left; **IFG**=inferior frontal gyrus; **preSMA**=pre-supplementary motor area. All degrees of freedom=29. Note that Holm-Bonferonni correction was conducted across all ROIs including subcortical ROIs reported in Chapter 3 (Section 3.2.1.2). α calculated as: α(*k*)=0.05/(*n*-*k*+1), where *n* is the number of ROIs (in this case 16), and *k* is the rank ordering of *p*-values from 1 to *n.* $^{++}$=non-parametric analysis required for pre-vs. post analysis (for correlation SOA Spearman's correlations were conducted and rs values subjected to one-sample t-tests (see APP10.4.4.2.2.3).

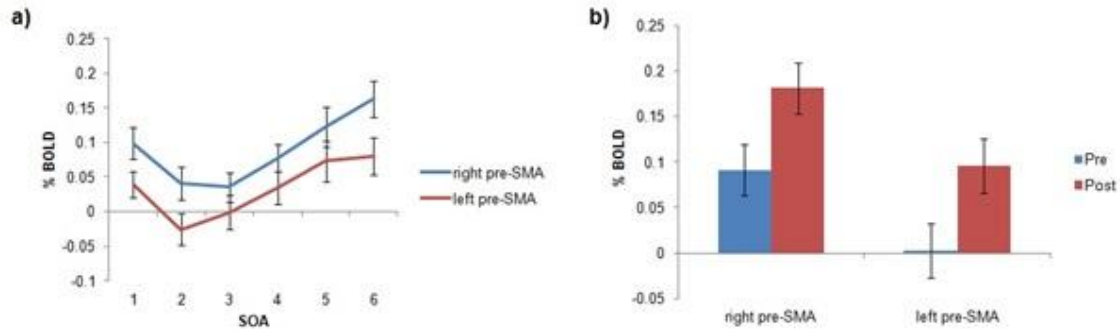


Figure 2.10. Change in %BOLD with SOA. **(a)** %BOLD in left and right pre-SMA with increasing SOA (where 1 is the shortest SOA and 6 is the longest); **(b)** %BOLD in the right pre-SMA and left pre-SMA when stop signals were presented within or post decision bottleneck. Error bars= ±1 within subject standard error (Cousineau, 2005; with correction, Morey, 2008).

2.4.4. Lateralisation of action updating

To investigate hemispheric specialisation, I explored whether right and left ROIs were differentially recruited under inhibitory and non-inhibitory action updating conditions, separately. %BOLD was drawn from each ROI for signal>no-signal contrasts in the SST and DT. Results are summarised in Table 2.10. As anticipated, inhibitory action updating (stop signal>stop no-signal) was generally associated with increased activity in right ROIs relative to left ROIs. Activity was also found to be greater in right relative to left IFG and right relative to left pre-SMA under conditions of non-inhibitory action updating (double signal>double no-signal). Although the rIFG (as well as the lIFG) has been previously implicated as a potential structural bottleneck (e.g. Herath *et al., 2*005; Jiang, 2004), it is likely this right-lateralised activity is associated with attention (Corbetta & Shulman, 2002; Corbetta *et al., 2*008), as opposed to action updating. This interpretation would account for the absence of brain-behaviour relationships between the rIFG and indices of non-inhibitory action updating (i.e. DRT2 and the size of the PRP; Section 2.4.3.2).

Table 2.10. Paired sample t-tests between right and left ROIs under inhibitory and non-inhibitory action updating conditions.

Contrast	ROI	Hemisphere	t	*p*	α	BF
Stop signal>	IFG	Right	**6.82**	<.001	.0063	**89773.71**
stop no-signal	pre-SMA	Right	**6.76**	<.001	.0071	**77430.59**
Double-signal>	IFG	Right	**5.52**	<.001	.0063	**3417.5**
double no-signal	pre-SMA	Right	**5.32**	<.001	.0071	**2007.07**

Note. **ROI**= region of interest, **Hemisphere**=the hemisphere for which the corresponding ROI demonstrated the greatest %BOLD; **t**=t-value, significant t-values are reported in bold; ***p***=p-value; **α**= alpha level; **BF**=Bayes Factors, BFs>3 are reported in bold; **IFG**=inferior frontal gyrus; **preSMA**=pre-supplementary motor area**.** All degrees of freedom=29. Note that Holm-Bonferonni correction was computed for all ROI analyses- including those reported in Chapter 3 (Section 3.2.1.3). α calculated as: $\alpha(k)=0.05/(n-k+1)$, where n is the number of ROIs (8 for both SST and DT analyses), and k is the rank ordering of p-values from 1 to n.

2.5. Discussion

The primary aim of this study was to establish the neuroanatomical distribution of inhibitory and non-inhibitory action updating. The results demonstrate the presence of a broad network which acts to support general processes common to different forms of

action updating, in addition to more specialised activity underlying inhibitory control. In accord with recent work the requirement to update action plans was met with common activity at the whole brain level (Chatham *et al.,* 2012; Dodds *et al.,* 2011; Erika-Florence *et al.,* 2014; Hampshire, 2015; Tabu *et al.,* 2011), including the pre-SMA and posterior rIFG, the *pars opercularis* (see Figure 2.5). Exclusive patterns of activity associated with distinct forms of action updating were found via disjunction analyses (see Figure 2.5). In particular, response inhibition uniquely recruited regions within the right frontal lobe. Specifically, the anterior rIFG, the *pars triangularis*, was activated to a greater extent when cancelling action plans as opposed to adding to pre-existing action plans.

The differential recruitment of the *pars triangularis* under SST relative to DT conditions suggests the potential for functional specialisation of the rIFG in implementing response inhibition. This indication is surprising given the inhibitory module has been proposed to lie within the *pars opercularis* (Aron *et al., 2*014a, 2014b) and recent imaging studies have established overlapping activity across the rIFG under both inhibitory and non-inhibitory action updating conditions (Chatham *et al.,* 2012; Dodds *et al.,* 2011; Erika-Florence *et al.,* 2014; Hampshire, 2015; Tabu *et al.,* 2011). These studies found no regional specificity associated with performance of the SST relative to control tasks.

The discrepancies between my findings and those in previous studies (Chatham *et al.,* 2012; Dodds *et al.,* 2011; Erika-Florence *et al.,* 2014; Hampshire, 2015; Tabu *et al.,* 2011) may be due to the differences in the way in which the tasks were employed. Such differences are likely related to response control requirements. For example, in imaging studies that have employed both SST and DT, signal presentation is generally less frequent than presented in the context-cueing paradigm (Study 1: 33% of trials, relative to Chatham *et al., 2*012: 25%; Erika-Florence *et al., 2*014: 26%; Hampshire *et al., 2*010: 26%; Hampshire *et al., 2*015: 25%). Also, within each of these studies, participants performed a single block of each task rather than multiple blocks as presented in the context-cueing paradigm. Thus, there may have been less learning-related effects (particularly given the thorough training procedure employed in the current study; see Section 2.2.3). Additionally, in Chatham *et al.'*s (2012) study, participants always completed the DT before the SST, and consequently the DT was

likely associated with greater task novelty[52]. Finally, the *complex* task employed by Erika-Florence *et al.* (2014) and Hampshire (2015; Figure 1.12), likely required greater task monitoring and working memory demands than provided by either task comprising the context-cueing paradigm. In the *complex* task, participants were required to monitor the presentation of frequent arrows pointing either left or right and to respond to infrequent targets- arrows facing upwards or downwards presented after a variable delay. Single responses were required to arrows facing upwards and a double-response to arrows facing downwards. Furthermore, the response to be executed on the upward facing arrows corresponded to the direction of the arrow preceding it, thus inducing conflicts between arrow direction representations and responses. Together, these methodological dissimilarities indicate the potential for a role of the rIFG in response control (or action updating demands) as opposed to the specific implementation of response inhibition.

Consistent with this interpretation, activity in the rIFG has been argued to be the result of task complexities and time-pressures when action cancellation is required in the SST as opposed to inhibition *per se* (Hughes *et al., 2*013; see also Criaud and Boulinguez, 2013; Simmonds *et al.,* 2008; Swick, Ashley, & Turken, 2011) and may be associated with the proposed hierarchical organisation of the frontal lobes along the caudal-rostral axis (see Badre & D'Esposito, 2009 and Botvinick, 2008, for reviews). These suggestions are also in-keeping with Levy & Wagner's (2011) meta-analysis that indicates the *pars opercularis* is associated with action updating requirements and the *pars triangularis* with ambiguous responding. Where, the conflicting task instructions in the SST (i.e. respond with speed, but stop upon presentation of a signal) likely to lead to uncertainty. I explore the potential for differences in task-related difficulty further in Chapter 6.

In general, overall patterns of activity for inhibitory and non-inhibitory action updating were consistent with expectations, with right lateralised fronto-parietal activity underlying response inhibition (e.g. Aron *et al., 2007*; Aron & Poldrack, 2006; Cai & Leung, 2011; Kenner *et al.,* 2010; see also reviews: Aron 2007, 2011; Banich & Depue, 2015) and bilateral fronto-parietal activity underlying double-responding (Collette *et al., 2*005; Dux *et al.,* 2006; Erickson *et al.,* 2005; Herath *et al.,* 2001; Jiang, 2004; Marois *et*

[52] As the stimuli comprising the SST and DT were the same, it is likely the novelty effects were lower in the SST as participants would have some experience of the task (at least with respect to stimulus and signal presentation and response keys).

al., 2006; Schubert & Szameitat, 2003; Sigman & Dehaene, 2008; Szameitat *et al.,* 2002). Common activity was found in right-lateralised regions, including the IFG and pre-SMA (owing to the right lateralised activity under SST, relative to DT conditions). As anticipated, the majority of the *pars opercularis* was recruited by both inhibitory and non-inhibitory action updating demands, for which previous work has attributed a causal role in general action updating (Verbruggen *et al., 2*010; Dippel & Beste, 2015; see also Chambers *et al.,* 2006, 2007; Dambacher *et al.,* 2014). Greater activity in the right, relative to left, IFG and in the right, relative to left, pre-SMA was established under both inhibitory and non-inhibitory action updating conditions. These activation patterns are consistent with a right-lateralised attention network (Corbetta & Shulman, 2002; Corbetta *et al.,* 2008), which would precede successful response control across both the SST and DT to enable the implementation of top-down response control (Miller & Cohen, 2001).

The pre-SMA was found to be recruited under both SST and DT conditions, supporting its conceptualisation as a 'flexible hub' that acts to support multiple cognitive control processes (Criaud & Boulinguez, 2013; Swick, Ashley, Turken, 2011). Given %BOLD in the pre-SMA was not found to differ between signal and no-signal trials in the IT, it is possible that the flexibility of the pre-SMA is only demonstrated when action plans require adjustment as opposed to the detection of infrequent, yet salient, signals. The generality of the pre-SMA is upheld by the brain-behaviour analyses that considered the delay between the stimulus and signal onset in both the SST and DT. In both tasks, pre-SMA activity was found to increase with increasing delay. In the SST, response conflict between stop and go processes and error likelihood is greater at longer relative to short SSDs (because the cancellation of the ongoing response is less likely; Logan & Cowan, 1984) and thus the pre-SMA may be associated with conflict resolution or performance monitoring (e.g. Taylor *et al., 2*007). However, this interpretation is inconsistent with the pattern of activity associated with the DT. If the pre-SMA involvement was simply due to differential control demands, it would be anticipated that activity would be greater at short relative to long SOAs, where structural or strategic bottleneck limitations would apply (e.g. Dux *et al.,*2006, 2009). Alternatively, it is possible that the pre-SMA is recruited under conditions where fast adjustments to action plans are required (Forstmann *et al.,* 2008; Ridderinkhof *et al.,* 2004), particularly where preparatory control is minimal (Jahfari *et al.,* 2012). The

potential for modification of response settings supports the similar patterns of activity across both the SST and DT.

In both the SST and DT, no correlations between %BOLD and the latencies of the updating processes were observed. The possible lack of effects may be associated with sample size. Although an N of 30 in fMRI research is typically considered large (Desmond & Glover, 2002; Friston, 2012; Friston, Holmes, & Worsley, 1999), and greater than that of similar studies (e.g. Chatham *et al., 2*012; Dodds et al., 2011; Erika-Florence *et al., 2*014; Hampshire *et al., 2*010; Hampshire, 2015), it is known that the replication of ROI-based results is challenging (see Boekel, Forstmann, & Wagenmakers, 2015; Boekel, Wagenmakers, Belay *et al.,* 2015; see also Poldrack & Mumford, 2009). Furthermore, previous findings in small studies may be unreliable (Button *et al.,* 2013) and there is much potential for reporting bias (David *et al.,* 2013). It is possible that this may explain the discrepancies in findings between studies.

In spite of the limitations of the current study, there also several methodological advantages. Primarily, this study presents the first fMRI study in this field to be pre-registered, and in detail (https://osf.io/zbk3p/). All methods, analyses and hypotheses were specified *a priori* (unless otherwise specified) and transparency is essential in overcoming the reporting bias in fMRI research and neuroscience more generally (David *et al., 2*013; Button *et al., 2*013). Furthermore, the study provides a replication of previous work that suggests a broad network of activity that supports response control processes (e.g. Hampshire, 2015; Hampshire & Sharp, 2015a, 2015b) and the generality of the pre-SMA in action updating (Criaud & Boulinguez, 2013; Forstmann *et al.,* 2008; Ridderinkhof *et al.,* 2004; Swick *et al.,* 2011).

In summary, the evidence presented here is consistent with a distributed fronto-parietal network of activity previously found to underlie general action updating processes (Hampshire, 2015; Hampshire & Sharp, 2015a, 2015b). However, the specific engagement of the *pars triangularis* under SST conditions is consistent with the proposal of a specialised role for rIFG sub-regions in the implementation of response inhibition (Aron *et al.,* 2003, 2007, 2014a, 2014b, 2015; Aron & Poldrack, 2006; Aron, 2011). To fully delineate the role of the rIFG and pre-SMA in response control, it is imperative to explore the activity within these regions under different response control conditions in relation to sub-regions of the BG - the targets of top down action control (Miller & Cohen, 2001). This investigation is the focus of Chapter 3.

Chapter 3. Study 1, Part II

Functional specialisation of cortical and subcortical structures underlying response execution and response inhibition

3.1. Introduction

Wide-spread interconnectivity is apparent between the frontal cortex, BG and thalamic structures (e.g. Aron *et al., 2*007; Forstmann *et al., 2*012; Jahfari *et al.,* 2011; Haynes & Haber 2013; Rae *et al., 2*015), and the control of motor responses is thought to involve the integrated activity of this fronto-subcortical network (Aron & Poldrack, 2006; Aron *et al., 2*007; Jahafari *et al., 2*011; Forstmann *et al., 2*012; Rae *et al., 2*015). Specifically, motor output through the thalamus (THAL) may be modulated by control signals originating from cortical regions such as the rIFG and pre-SMA (Wiecki & Frank, 2011; Schroll & Hamker, 2013) by way of three putative pathways through the BG: the direct, indirect and hyperdirect pathways (Albin *et al.,* 1989; Alexander & Crutcher, 1990; Nambu *et al.,* 2002; see Figure 3.1). To produce a motor response, a fronto-striatal-pallidal (direct) pathway is activated, which can be blocked when inhibition is required via the indirect or hyperdirect pathway. Response inhibition is thought to operate through the Subthalamic Nucleus (STN), Substantia Nigra (SN) and Globus Pallidus interna (GPi) to suppress thalamic output (Albin *et al.,* 1989; Alexander & Crutcher, 1990; Nambu *et al., 2*002). The hyperdirect pathway is so-called because it operates via direct cortical projections to the STN, which results in fast, reactive inhibition (Aron & Poldrack, 2006; Aron *et al., 2*007; Nambu *et al., 2*002). In comparison, the indirect route involves projections to the Striatum (STR) and the external segment of the Globus Pallidus (GPe) before reaching the STN to decrease thalamico-cortico output (Albin *et al.,* 1989; Alexander & Crutcher, 1990). This slower route is theorised to provide tonic suppression when there is sufficient time to plan the withholding of actions (i.e. proactive inhibition) and may be more selective (see also Aron, 2011 and Greenhouse *et al.,* 2012).

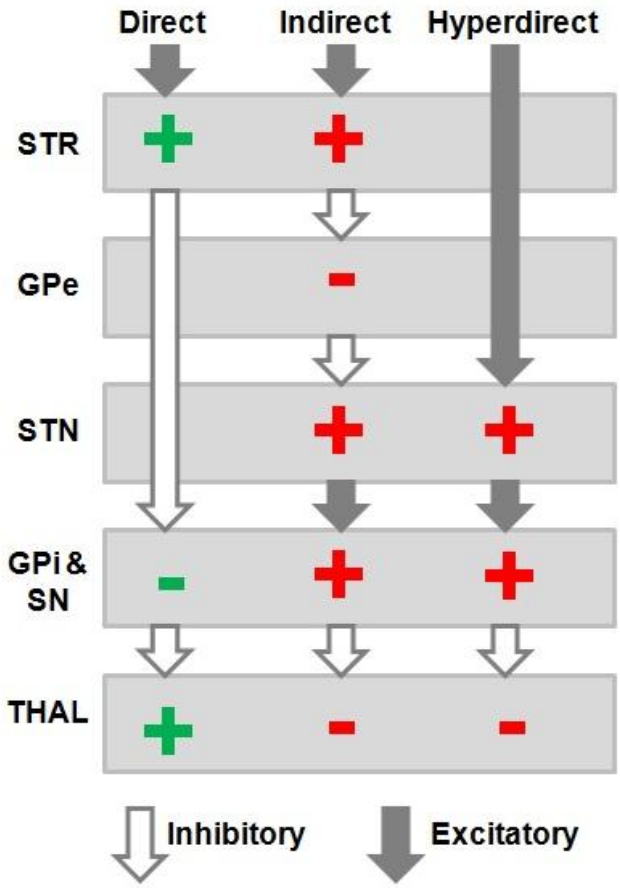


Figure 3.1. Schematic of the cortico-subcortical pathways model of response execution and response inhibition (Albin *et al.,* 1989; Alexander & Crutcher, 1990; Nambu *et al.,* 2002). White arrows represent inhibitory projections and grey arrows represent excitatory projections. + symbols indicate up-regulation of activity and – symbols indicate down-regulation of activity within specified structures of each pathway. Green symbols refer to response execution and red symbols refer to response inhibition. The *direct* pathway is theorised to enable responses to be executed, triggered via excitatory projections from the frontal cortex received by the striatum (STR), which in turn sends inhibitory projections to the globus pallidus interna (GPi) and the substantia nigra (SN). The *indirect* and *hyperdirect* pathways are proposed to block the execution of actions of the direct pathway via the subthalamic nucleus (STN). The *indirect* pathway involves inhibitory projections from the STR to the globus pallidus externa (GPe). This reduces the inhibitory effects exerted on the STN, increasing excitation to the GPi and SN, which in turn inhibit activity in the thalamus (THAL). The *hyperdirect* pathway is a faster mechanism in which direct frontal input is received by the STN (bypassing the STR), which sends excitatory output to the GPi/SN, inhibiting the THAL.

As outlined in Chapter 1 (Section 1.2.3), support for the role of BG in action control has arisen from a number of sources. For example, lesions to regions hypothesised to be crucial for the cancellation of actions, including the STR (Eagle and Robbins, 2003) STN (Baunez, Humby, Eagle *et al.,* 2001; Rieger *et al., 2*003; but see Eagle *et al.,* 2008) and GP (Ryan & Sanders, 1994; Thompson, Harmon, & Yu, 1985) cause impairments in response inhibition. Furthermore, dysfunctional activity and

abnormalities of the BG are known to underlie the motor symptoms associated with different disorders, including Tourette's syndrome, and Huntington's and Parkinson's Disease (see reviews: Middleton & Strick, 2000; Mink, 2001; Utter & Basso, 2008). Under conditions of response inhibition, imaging studies have found differences in reactivity of the rIFG, medial frontal cortex and BG structures in individuals with varying inhibitory abilities (Aron & Poldrack, 2006; Aron *et al., 2*007; Li *et al.,* 2006, 2008; Sharp *et al.,* 2010; Chao *et al.,* 2009) and when probability of signal presentation is manipulated (Chikazoe *et al.,* 2009; Jahfari *et al.,* 2011, 2012; Majid *et al.,* 2013; Smittenaar, Guitart-Masip, Lutti, & Dolan, 2013; Vink *et al*., 2005; Wijeakumar, Magnotta, Buss *et al.,* 2015; Zandbelt & Vink, 2010). Correlations between activity in these structures and SSRT have been found (Aron & Poldrack, 2006; Aron *et al., 2*007; Mayse, Nelson, Park, Gallagher, & Lin, 2014; although see Forstmann *et al., 2*012). Both anatomical and effective connectivity are also evident (e.g. Aron *et al., 2*007; Forstmann *et al.,* 2010; Forstmann *et al., 2*012; Jahfari *et al.,* 2011; Duann *et al.,* 2009). Due to the direct efferent connectivity from the cortex, previous research has largely focused on the role of the STR and STN in response inhibition (e.g. Aron, Behrens, Smith, Frank, & Poldrack, 2007; Aron & Poldrack, 2006; Forstmann *et al.,* 2008, 2012; Jahfari *et al.,* 2011; van Belle *et al.,* 2014; Vink *et al.,* 2015; Zandbelt & Vink, 2010; Vink *et al., 2*005; Zandbelt *et al., 2*013). However, to fully delineate how the BG may act to implement response control in the human brain our investigations must extend beyond these regions in isolation and explore the contribution of the BG circuitry in its entirety under different response-control conditions. Such research may alleviate some of the controversy over the specificity of the pathways in terms of behavioural inhibition, and more fundamentally their existence (Hampshire & Sharp, 2015; Hampshire, 2015; Bahuguna *et al.*, 2015; see Calibrisi *et al., 2*014, for a review). There is also the question of how (and if) these pathways are detectable using fMRI.

Here, data acquired for Study 1 were initially subjected to pre-registered brain-behaviour analysis as per Section 2.4.3, to assess whether subcortical reactivity was related to behavioural indices of action updating. However, this chapter primarily focuses on the results of exploratory analyses aimed to ascertain whether the observed pattern of sub-cortical activations and deactivations, as predicted by the theoretical excitatory and inhibitory inputs of the pathways models, were expressed under behaviourally relevant conditions. For example, if the hyperdirect pathway is

responsible for response inhibition then I expected to observe increased STN, SN and GPi activity and decreased THAL[53] activity in the presence of a stop signal (Figure 3.1).

Additionally, I explored whether the functional specificity of each pathway was lateralised to either hemisphere. Although lateralisation of function was not proposed by the original pathways models (Albin *et al., 1*989; Alexander & Crutcher, 1990; Nambu *et al.,* 2002), the lateralisation of motor execution has been found in previous work (e.g. Solodkin, Hlustik, Noll, & Small, 2001) and abnormalities of the STN are known to result in symptoms to limbs on the contralateral side (e.g. as in hemiballism and Parkinson's disease, Pirker, Holler, Gerschlager *et al., 2*003; Whittier & Metler, 1949; Wu, Hou, Hallett *et al.,* 2015). Furthermore, as will be reported, I also observed subcortical lateralisation underlying inhibitory (right-lateralised) and non-inhibitory (left-lateralised) action updating under differerent response control conditions.

Finally, analyses examined the interrelations between structures, to assess the direction of influence of activity between regions under conditions of response execution and response inhibition.

3.2. Statistical analysis and results

Given the differences in the aims of this chapter, I report the statistical analyses and results pertaining to the brain-behaviour relationships separately from the exploration of the pathways models.

3.2.1. Brain-behaviour relationships

The analyses reported within this section were pre-registered. Brain-behaviour analyses sought to determine whether %BOLD associated with response inhibition and non-inhibitory action updating varied in accordance with behavioural indices of response control: including the efficiency of action updating (as measured via SSRT and DRT2) and when signals were presented (i.e. before or after 50%SSD and within or post-

[53] Here, it was anticipated that decreased neuronal activity be reflected in a reduction in BOLD signal. Although the relationship between neuronal activity and hemodynamics is unclear (Logothetis, 2008; Lauritzen, Mathiesen, Schaefer, & Thomsen, 2012), previous research has shown BOLD activity to be correlated with changes in local field potentials and related to functional inhibition (e.g. Kastrup, Baudewig, Schaudigel *et al.,* 2008; Schäfer, Blankenberg, Kupers *et al.,* 2012).

bottleneck, or variable with SSD/SOA). Additional analyses explored whether %BOLD in the DT varied with the size of the PRP as measured via the quantification procedure outlined in Section 2.3.1. Extraction of %BOLD and data screening were as outlined in Sections 2.3.2.2 and 2.3.3.

Regions of interest (ROI) were defined *a priori*. The STR, GPe, GPi, STN and SN were defined as the corresponding regions in the atlas of the BG (ATAG; Keuken, Bazin, Crown *et al*., 2014; all thresholded at 25%). The THAL was as specified by the Harvard-Oxford sub-cortical atlas (thresholded at 25%). All masks were linearly transformed into MNI space using FLIRT in FSL prior to thresholding and binarised using fslmaths before interrogation with Featquery.

Analyses are reported separately for inhibitory and non-inhibitory action updating. Parametric analyses and Bayesian equivalents are reported here. Non-parametric analyses (where required) and analyses subsequent to outlier removal are reported in APP10.2.1. Any discrepancies between findings are discussed.

3.2.1.1. Relationships between indices of inhibitory action updating and %BOLD

As outlined in Sections 2.1.2.1 and 2.4.3.4, SSRT was anticipated to correlate negatively with %BOLD in regions crucial for response inhibition, as per previous work (e.g. Aron *et al.*, 2007; Aron & Poldrack, 2006). As for cortical structures, %BOLD in subcortical regions was found to generally increase with SSRT (Table 3.1). While indicating recruitment increased with more effortful (or less efficient) response inhibition, BFs indicate no substantial evidence for this effect. As found for cortical sites of interest, no relationships between %BOLD and proactive slowing were identified (Table 3.1) and thus are unlikely to explain the absence of relationships with SSRT.

Table 3.1. Correlations between %BOLD in subcortical ROIs acquired from the contrast stop signal>stop no-signal with SSRT and proactive slowing.

	Mean SSRT				Integration SSRT			Proactive Slowing[+]		
ROI	r	*p*	α	BF	r	*p*	BF	r	*p*	BF
R STR	0.37	.044		1.32	0.34	.069	0.96	-0.18	.339	0.3
R GPe	0.36	.048		1.19	0.32	.086	0.79	-0.13	.504	0.24
R GPi	0.13	.510		0.24	0.09	.654	0.22	0.01	.976	0.19
R STN	0.05	.806		0.2	-0.05	.814	0.2	0.03	.865	0.2
R SN[++]	0.18	.331		0.3	0.11	.566	0.23	0.09	.621	0.22
R THAL[+]	-0.27	.156		0.52	0.25	.189	0.45	0.09	.649	0.22
L STR	0.26	.169		0.48	0.21	.266	0.35	-0.05	.797	0.2
L GPe	0.36	.053		1.19	0.29	.126	0.61	-0.07	.722	0.21
L GPi	0.33	.077		0.87	0.26	.173	0.48	-0.08	.672	0.21
L STN[+]	0.18	.352		0.3	-0.01	.947	0.19	-0.06	.769	0.2
L SN[++]	0.43	.017	.0028	2.8	0.34	.062	0.96	0.08	.682	0.21
L THAL	0.21	.263		0.35	0.19	.326	0.31	0.07	.724	0.21

Note. Stop signal reaction time (**SSRT**) was estimated using the mean and integration methods, separately. **ROI**=region of interest; **r**=Pearson's correlation coefficient; ***p***= *p*-value; **BF**=Bayes Factor; **R**=right; **L**=left; **STR**= striatum; **GPe**= globus pallidus externa; **GPi**= globus pallidus interna; **STN**= subthalamic nucleus; **SN**= substantia nigra; **THAL**= thalamus; [+]= computed on transformed data; [++]= non-parametric required. All degrees of freedom=28. Note that Holm-Bonferonni correction was computed for all ROI analyses- including those reported in Chapter 2 (section 2.4.3.1). α calculated as: $\alpha(k)=0.05/(n-k+1)$, where *n* is the number of ROIs (in this case 18), and *k* is the rank ordering of *p*-values from 1 to *n.*

Due to the non-normal (slightly bimodal) distribution of SSRT estimates observed in the current study (Figure 2.8) data were also analysed within independent t-tests subsequent to median split. Greater %BOLD was found in participants with long vs. short SSRTs in the right STR, right GPe and left GPe using both the mean and integration methods (Table 3.2). Outlier exclusion (Table APP10.2.2.) reduced the evidence in favour of a difference in right STR (mean method: BF=2.16; integration method: BF=1.28); however the relationships persisted for bilateral GPe. Whether these regions play an integral role in response inhibition requires exploration of the activity in this region under non-inhibitory action updating conditions.

Table 3.2. Differences in %BOLD in subcortical ROIs between participants with short vs. long SSRTs. Independent t-tests were conducted subsequent to median split of SSRT.

	Mean SSRT				Integration SSRT			
ROI	t	*p*	α	BF	t	*p*	α	BF
R STR$^{++◊◊}$	-2.52	.018		**3.3**	-2.47	.02		**3.08**
R GPe$^{++◊◊}$	-2.79	.01	.0028	**5.23**	-2.78	.01	.0028	**5.2**
R GPi	-1.21	.239		0.61	-0.7	.489		0.42
R STN$^{++◊◊}$	-0.46	.647		0.38	-0.3	.765		0.36
R SN$^{++◊}$	-0.43	.675		0.38	0.63	.535		0.4
R THAL	-2.15	.041		1.84	-1.68	.104		0.98
L STR$^{◊◊}$	-2.03	.053		1.56	-2.05	.049		1.61
L GPe	-2.56	.017		**3.49**	-2.72	.011		**4.66**
L GPi	-1.79	.086		1.13	-1.47	.152		0.77
L STN$^{+◊◊}$	9.35	.339		0.49	-0.66	.514		0.41
L SN$^{++◊◊}$	-1.91	.067		1.33	-2.33	.027		2.45
L THAL	-1.69	.102		1.01	-1.56	.129		0.85

Note. Stop signal reaction time (**SSRT**) was estimated using the mean and integration methods, separately. **ROI**=region of interest; **t=**t-value; ***p***=p-value; **α**=alpha-level; **BF**=Bayes Factor, BFs>3 reported in bold; **R**=right; **L**=left; **STR**=striatum; **GPe**=globus pallidus externa**; GPi**= globus pallidus interna; **STN**= subthalamic nucleus; **SN**=substantia nigra; **THAL**=thalamus; $^{+}$ and $^{◊}$= analysis conducted on transformed data when SSRTs were estimated using the mean and integration methods, respectively; $^{++}$ and $^{◊◊}$=non-parametric analysis required when SSRT was estimated using the mean and integration methods, respectively. 2 participants SSRT were equal to the median value when estimated using the mean method and were excluded from this analysis. Degrees of freedom= 26 for analysis using the mean method, and 28 for analysis using the integration method. Holm-Bonferonni correction was computed for all ROI analyses- including those reported in Chapter 2 (section 2.4.3.1). α calculated as: $\alpha(k)=0.05/(n-k+1)$, where n is the number of ROIs (in this case 18), and k is the rank ordering of p-values from 1 to n.

As increasing the duration between stimulus and signal onsets in the SST reduces the probability of successful inhibition (Logan & Cowan, 1984) I anticipated differences in activity in those ROIs crucial to response inhibition as a function of stop success. Evidence for a relationship between %BOLD and SSD was found in bilateral THAL (Table 3.3, Figure 3.2a). These regions were found to be recruited to a greater extent as SSD increased. Similarly, activity was also found to be greater in the left THAL when signals were presented after the 50%SSD (i.e. long SSDs where there was a low probability of stop signal success) relative to when signals were presented prior to the 50%SSD (i.e. short SSDs where there was a high probability of stop signal success; Table 3.3, Figure 3.2b)[54]. It is possible that the THAL reacts to either the increased effort to cancel an action or increased attentional processes associated with error and performance monitoring when stop signal success is limited.

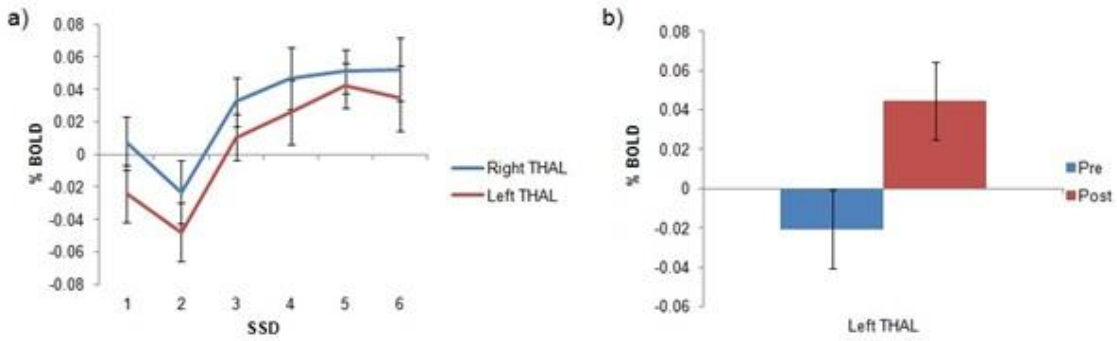


Figure 3.2. Change in %BOLD with SSD. **(a)** %BOLD in left and right THAL with increasing SSD (where 1 is the shortest SSD and 6 is the longest). **(b)** %BOLD in the left THAL when stop signals were presented before or after the 50%SSD. For these analyses *p*-values did not survive correction for multiple comparisons, but BFs were >3 indicating substantial evidence for an effect. Error bars= ±1 within subject standard error (Cousineau, 2005; with correction, Morey, 2008).

[54] Outlier exclusion also yielded strong BFs for left SN. However, %BOLD in this region was found to violate the assumption of normality and non-parametric analysis found this differential recruitment to be non-significant.

Table 3.3. One-sample t-tests of coefficients yielded from within-subject correlations across SSDs and paired sample t-tests between %BOLD when stop signals were presented before or after the 50%SSD.

	Correlation SSD++				Pre vs. post 50%SSD			
ROI	t	*p*	α	BF	t	*p*	α	BF
R STR++	1.21	.238		0.38	-0.33	.747		0.2
R GPe	1.26	.217		0.4	-1.25	.220		0.4
R GPi	0.87	.394		0.27	-0.89	.383		0.28
R STN	0.77	.448		0.26	-1.06	.299		0.32
R SN	1.58	.125		0.59	-1.36	.183		1.92
R THAL	2.74	.010		**4.33**	-2.39	.024		2.19
L STR	0.84	.410		0.27	-0.35	.729		0.21
L GPe	1.58	.125		0.59	-1.37	.180		0.46
L GPi	0.99	.329		0.31	-1.73	.095		0.73
L STN++	1.98	.058		1.07	-1.44	.161		0.49
L SN++	2.18	.038		1.49	-1.92	.065		0.98
L THAL	3.19	.003	.0029	**11.23**	-3.28	.003	.0029	**13.81**

Note. **Correlation SSD**: as within-subject %BOLD across SSDs were highly correlated, separate correlations were conducted for each participant and each ROI. Resultant Pearson's coefficients were subjected to either Frequentist or Bayesian one-sample t-tests to ascertain whether there was an effect of increasing delay between stimulus and signal. **Pre- vs. post 50%SSD** refers to the results of paired sample t-tests when signals were presented before or after the 50%SSD. **ROI**=region of interest; **t=**t-value; ***p***=p-value; **α**= alpha-level; **BF**=Bayes Factor, BFs>3 reported in bold; **R**=right; **L**=left; **STR**=striatum; **GPe**=globus pallidus externa; **GPi**=globus pallidus interna; **STN**=subthalamic nucleus; **SN**=substantia nigra; **THAL**=thalamus. All degrees of freedom=29. Note that Holm-Bonferonni correction was conducted across all ROIs including subcortical ROIs reported in Chapter 2 (Section 2.4.3.1). α calculated as: $\alpha(k)=0.05/(n-k+1)$, where n is the number of ROIs (in this case 18), and k is the rank ordering of p-values from 1 to n. ++=non-parametric analysis required for pre-vs. post analysis (for correlation SOA Spearman's correlations were conducted and rs values subjected to one-sample t-tests (see APP10.2.1.1.3).

3.2.1.2. Relationships between indices of non-inhibitory action updating and %BOLD

It was anticipated that regions crucial to non-inhibitory action updating would be recruited to a greater extent in those with long DRT2s due less efficient updating capabilities and a greater influence of the PRP (e.g. Collette *et al.*, 2005; Dux *et al.*, 2006; Herath *et al.*, 2001; Jiang, 2004; Marois *et al.*, 2006; Schubert & Szameitat, 2003; Sigman & Dehaene, 2008; Szameitat *et al.*, 2002; Tombu *et al.*, 2011). However, no relationships were observed between DRT2, the size of the PRP and %BOLD in any

subcortical ROIs (Table 3.4). BFs indicate evidence largely in favour of the null. Thus it appears unlikely that these ROIs impose structural limitations on decision-making processes in the DT.

Table 3.4. Correlations between %BOLD in subcortical ROIs acquired from the contrast double signal>double no-signal with DRT2 and estimated size of the PRP.

	DRT2			Size		
ROI	r	*p*	BF	r	*p*	BF
R STR	-0.18	.353	0.3	-0.04	.817	0.2
R GPe	-0.17	.373	0.28	-0.03	.89	0.2
R GPi^{++}	0.02	.906	0.2	0.06	.736	0.2
R STN	-0.2	.285	0.33	-0.09	.645	0.21
R SN	-0.31	.094	0.72	-0.04	.833	0.2
R THAL	-0.2	.299	0.33	0.16	.411	0.27
L STR	-0.26	.173	0.48	-0.12	.513	0.23
L GPe	-0.1	.611	0.22	0.03	.876	0.2
L GPi	-0.1	.602	0.22	0.01	.947	0.19
L STN	-0.28	.14	0.56	-0.12	.539	0.23
L SN	-0.14	.477	0.25	-0.11	.566	0.23
L THAL	-0.16	.386	0.27	0.13	.511	0.24

Note. **DRT2**=the latency of the non-inhibitory action updating process; **Size**=size of the PRP; **ROI**= region of interest, **r=** Pearson's correlation coefficient; ***p***=p-value; **BF**=Bayes Factor; **R**=right; **L**=left; **STR**=striatum; **GPe**=globus pallidus externa; **GPi**=globus pallidus interna; **STN**=subthalamic nucleus; **SN**=substantia nigra; **THAL**=thalamus; $^{++}$= non-parametric required for both DRT2 and Size analyses**.** α not shown as all *p*>.05. All degrees of freedom=28.

Median split of DRT2 revealed stronger ROI activity for participants with short relative to long DRT2s in the left STN (Table 3.5). Thus greater recruitment of the left STN may be reflective of greater updating efficiency under conditions where response inhibition is not required. Conversely, greater activity was revealed when the size of the PRP was small relative to large (Table 3.5), but evidence was not found to substantial for any of the subcortical ROIs explored. The role of the left STN is unclear, given its hypothesised role in response inhibition as opposed to response execution (Albin *et al.*, 1989; Alexander & Crutcher, 1990; Nambu *et al., 2*002b), but may be associated with response selection under high demands.

Table 3.5. Differences in %BOLD in subcortical ROIs between participants with short vs. long DRT2s and small vs. large PRPs. Independent t-tests were conducted subsequent to median split of DRT2 and size of PRP.

	DRT2					Size			
ROI	t	df	*p*	α	BF	t	df	*p*	BF
R STR	1.75	28	.091		1.07	0.25	25	.801	0.37
R GPe	1.57	28	.128		0.86	1.28	25	.212	0.65
R GPi$^{++\lozenge}$	0.27	28	.788		0.35	-0.72	25	.479	0.43
R STN	1.65	28	.111		0.94	0.02	25	.988	0.36
R SN$^{\lozenge\lozenge}$	2.15	28	.04		1.85	0.06	25	.955	0.36
R THAL	1.9	28	.069		1.29	-0.28	26	.779	0.37
L STR	1.89	28	.07		1.27	0.69	25	.497	0.43
L GPe	0.99	28	.332		0.5	0.54	25	.594	0.4
L GPi	0.93	28	.362		0.48	0.9	25	.38	0.48
L STN	2.74	28	.011	.0028	**4.9**	0.77	25	.451	0.45
L SN$^{\lozenge}$	1.86	28	.074		1.22	0.45	25	.628	0.39
L THAL	1.23	28	.229		0.61	-0.532	25	.599	0.4

Note. **DRT2=** the latency of the non-inhibitory updating process; **Size=**size of the PRP; **ROI**= region of interest, **t=** t-value, **df**=degrees of freedom, adjusted where Levene's test for homoscedasticity was significant; ***p***=p-value; **α**= alpha-level; **BF**=Bayes Factors, BFs>3 are reported in bold; **R**=right; **L**=left; **STR**=striatum; **GPe**=globus pallidus externa; **GPi**=globus pallidus interna; **STN**=subthalamic nucleus; **SN**=substantia nigra; **THAL**=thalamus**;** $^{+}$and $^{\lozenge}$= analysis conducted on transformed data for DRT2 and size data, respectively; $^{\lozenge\lozenge}$=non-parametric required (size data only). Size of the PRP for 3 participants was identical to the median and were excluded. Holm-Bonferonni correction was computed for all ROI analyses- including those reported in Chapter 2 (Section 2.4.3.2). α calculated as: $\alpha(k)=0.05/(n-k+1)$, where n is the number of ROIs (in this case 16), and k is the rank ordering of p-values from 1 to n.

In the DT, whether signals were presented within or after the bottleneck period was dependent on the SOA. Here, it was anticipated that increased SOA be associated with decreased %BOLD due to the reduction in demands in the post relative to the within-bottleneck period and that %BOLD associated with short SOAs be greater than long SOAs when separated into within and post-bottleneck periods, respectively. No evidence for subcortical involvement was observed (Table 3.6).

Table 3.6. One-sample t-tests of coefficients yielded from within-subject correlations across SOAs and paired sample t-tests between %BOLD when double signals were presented within or post decision bottleneck.

	Correlation SOA			Pre vs. post			
ROI	t	*p*	BF	t	*p*	α	BF
R STR^{++}	0.72	.476	0.25	-1.21	.234		0.38
R GPe	0.94	.354	0.29	-1.22	.232		0.38
R GPi	-1.07	.293	0.33	-0.22	.831		0.2
R STN^{++}	0.75	.462	0.25	-1.47	.154		0.51
R SN	0.97	.34	0.3	-2.19	.036	0.0036	1.54
R THAL	1.7	.1	0.7	-1.34	.192		0.44
L STR^{++}	0.19	.849	0.2	-1.23	.227		0.39
L GPe^{++}	0.87	.392	0.28	-1.69	.103		0.69
L GPi^{++}	0.04	.965	0.2	-0.75	.459		0.25
L STN	-0.09	.927	0.2	-0.64	.527		0.24
L SN^{++}	0.14	.892	0.2	-1.78	.085		0.79
L THAL	1.61	.119	0.61	-1.77	.087		0.78

Note. **Correlation SOA**: as within-subject %BOLD across SOAs were highly correlated, separate correlations were conducted for each participant and each ROI. Resultant Pearson's coefficients were subjected to either Frequentist or Bayesian one-sample t-tests to ascertain whether there was an effect of increasing delay between stimulus and signal. **Pre- vs. post** refers to the results of paired sample t-tests when signals were presented within or post-bottleneck. **ROI**=region of interest; **t=**t-value; ***p***=p-value; **α**= alpha-level; **BF**=Bayes Factor; **R**=right; **L**=left; **STR**=striatum; **GPe**=globus pallidus externa; **GPi**=globus pallidus interna; **STN**=subthalamic nucleus; **SN**=substantia nigra; **THAL**=thalamus. All degrees of freedom=29. Note that Holm-Bonferonni correction was conducted across all ROIs including subcortical ROIs reported in Chapter 3 (Section 2.4.3.2). α calculated as: $\alpha(k)=0.05/(n-k+1)$, where n is the number of ROIs (in this case 16), and k is the rank ordering of p-values from 1 to n. $^{++}$=non-parametric analysis required for pre-vs. post analysis (for correlation SOA Spearman's correlations were conducted and rs values subjected to one-sample t-tests (see APP10.2.1.2.3).

3.2.1.3. Lateralisation of action updating

To investigate hemispheric specialisation, I explored whether right and left ROIs were differentially recruited under inhibitory and non-inhibitory action updating conditions, separately. %BOLD was drawn from each ROI for signal>no-signal contrasts conducted in the SST and DT. Results are summarised in Table 3.7. As anticipated, inhibitory action updating (stop signal>stop no-signal) was generally associated with increased activity in right ROIs relative to left ROIs. Conversely, increased left ROIs relative to

right ROIs were associated with non-inhibitory action updating (double signal>double no-signal) [55].

Table 3.7. Paired sample t-tests between right and left ROIs under inhibitory and non-inhibitory action updating conditions.

Contrast	ROI	Hemisphere	t	*p*	α	BF
Stop signal> stop no-signal	STR	Right	**5.11**	<.001	.01	**1200.05**
	GPe^{+}	Left	0.09	.926		0.2
	GPi	Left	0.13	.900		0.2
	STN	Right	**2.75**	.010	.0125	**4.47**
	SN	Right	1.9	.067		0.95
	THAL	Right	**5.33**	<.001	.0083	**2074.76**
Double-signal> double no-signal	STR	Right	1.25	.221		0.4
	GPe^{++}	Left	1.51	.141		0.54
	GPi	Left	1.6	.121		0.61
	STN	Left	0.45	.656		0.21
	SN	Left	2.73	.011	.0083	**4.3**
	THAL	Left	1.09	.286		0.33

Note. **ROI**= region of interest, **Hemisphere**=the hemisphere for which the corresponding ROI demonstrated the greatest %BOLD; **t**=t-value, significant t-values are reported in bold; ***p***=p-value; **α**= alpha level; **BF**=Bayes Factors, BFs>3 are reported in bold; **STR**=striatum; **GPe**=globus pallidus externa; **GPi**=globus pallidus interna; **STN**=subthalamic nucleus; **SN**=substantia nigra; **THAL**=thalamus; $^{+}$ = analysis conducted on transformed data; $^{++}$ = non-parametric analysis required. Note that Holm-Bonferonni correction was computed for all ROI analyses- including those reported in Chapter 2 (Section 2.4.4). α calculated as: $\alpha(k)=0.05/(n-k+1)$, where n is the number of ROIs (in this case 8 for both stop and double contrasts), and k is the rank ordering of p-values from 1 to n.

3.2. Assessment and development of pathways models

The analyses presented in this section are exploratory and were not pre-registered. Here, I aimed to establish how well BOLD activity within the BG and THAL mirrored the pattern of activity predicted by behaviourally relevant action pathways (i.e. response execution and the direct pathway, response inhibition and the indirect and hyperdirect pathways). The analyses contained within this section aimed to assess how well BOLD activity within BG ROIs under different response control conditions conformed to that predicted by the neural pattern of the pathways models (Figure 3.1). As these analyses are highly exploratory and aim to establish what can be inferred from the overall pattern

[55] After outlier removal the right SN activity became significantly greater than left SN activity under conditions of inhibitory action updating, while the left SN no longer remained significantly greater than right SN activity under conditions of non-inhibitory action updating (Table APP10.2.9)

of BOLD activity within BG ROIs, frequentist analyses were not for multiple comparisons[56] and were conducted without outlier removal. The novel multi-analytic approach adopted is summarised in Figure 3.3. It is important to note that the analyses presented here assume that changes in neural activity and BOLD activity are within the same direction (i.e. up/down-regulation of neural activity is met with up/down-regulation of BOLD activity). Although the relationship between neuronal activity and hemodynamics is unclear (Logothetis, 2008; Lauritzen *et al.*, 2012), previous research has shown BOLD activity to be correlated with changes in local field potentials and related to functional inhibition (e.g. Kastrup *et al.*, 2008; Schäfer *et al.*, 2012).

As BOLD activity in the BG is notoriously difficult to uncover (Chevrier *et al.*, 2007), a novel approach to the fMRI analyses was developed, in which 203 separate contrast combinations were computed, including all reasonable contrasts that had the potential to inform the hypothesis in question. These were then divided into response execution or response inhibition (proactive or reactive[57]) categories prior to interrogation. Categorisation was completed independently by me and 2 other researchers[58]. Categories and corresponding contrasts are outlined in Table 3.8. %BOLD was averaged across all contrasts within a category for each ROI. As the differences between constitutive contrasts are not of interest (e.g. stop no-signal vs. null events) but the similarities are (e.g. the presence of a stop signal) averaging should theoretically result in variables that enhance statistical reliability and the stability of related inferences. As far as I am aware this cluster-based approach has not been conducted before.

[56] This decision was pre-registered prior to data collection.

[57] To clarify, proactive inhibition refers to the preparation to stop an action when there is sufficient time to plan the withholding of actions and is theorised to recruit the indirect pathway. Conversely, reactive inhibition refers to the fast implementation of stopping of all actions (Aron, 2011).

[58] Dr Christopher P.G. Allen (Cardiff University Brain Research Imagining Centre) and Dr Nils Muhlert (School of Psychological Sciences, Manchester University). Both of these researchers are familiar with the response inhibition literature. Labels were given if two or more researchers were in agreement with the category.

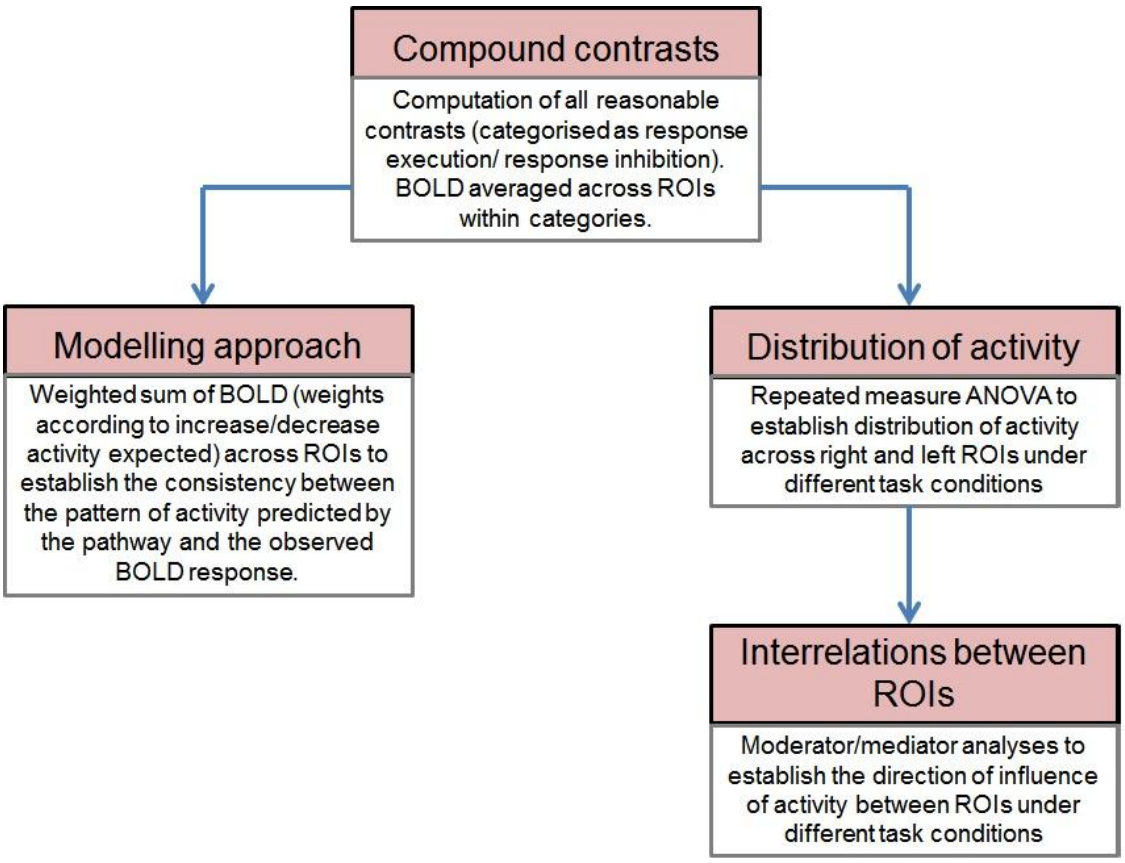


Figure 3.3. Summary of the stages of analysis aimed to explore the pattern of BOLD activity in BG ROIs under different response control conditions. Initially all events pertaining to each task (including the presentation of fixation crosses, no-signal and signal trials) were combined to produce 203 separate contrast combinations (compound contrasts). Contrasts were categorised as reflective of either response execution or response inhibition (see Table 3.8). For some analyses, contrasts pertaining to response inhibition were further subdivided into proactive and reactive inhibition categories. %BOLD was extracted from each ROI for each contrast for each individual subject. Subsequent analyses aimed to explore (1) how well the pattern of BOLD activity conformed to that predicted by the pathways models (the modelling approach), (2) the distribution of activity across ROIs under different response conditions, and (3) the interrelations of BOLD activity between ROIs under different response control conditions. To clarify, the modlling approach is independent of those analyses aimed at exploring the spatial distribution of activity under different response control conditions and those aimed at exploring the interrelations between ROIs.

Table 3.8. Table of computed contrasts and associated categorisation.

Response execution						Proactive inhibition				Reactive inhibition	
DA	IA	DS	DNS	IS	INS	FS	SA	SSI	SNS	SS	SSC
DA>SA	IA>SA	DS>SA	DNS>SA	IS>SA	INS>SA	FS>DA	SA>DA	SSI>FA	SNS>DA	SS>DA	SSC>SA
DA>IA	IA>FA	DS>IA	DNS>IA	IS>FA	INS>FA	FS>IA	SA>IA	SSI>FD	SNS>IA	SS>IA	SSC>DA
DA>FA	IA>FS	DS>FA	DNS>FA	IS>FS	INS>FS	FS>FD	SA>FA	SSI>FI	SNS>FA	SS>FA	SSC>IA
DA>FS	IA>FD	DS>FS	DNS>FS	IS>FD	INS>FD	FS>FI	SA>FD	SSI>DA	SNS>FD	SS>FS	SSC>FA
DA>FD	IA>FI	DS>FD	DNS>FD	IS>FI	INS>FI	FS>DS	SA>FI	SSI>IA	SNS>FI	SS>FD	SSC>FS
DA>FI	IA>SS	DS>FI	DNS>FI	IS>SS	INS>SS	FS>DNS	SA>DS	SSI>DS	SNS>DS	SS>FI	SSC>FD
DA>SS	IA>SNS	DS>SS	DNS>SS	IS>SNS	INS>SNS	FS>IS	SA>DNS	SSI>DNS	SNS>DNS	SS>SNS	SSC>FI
DA>SNS	IA>SSC	DS>SNS	DNS>SNS	IS>SSC	INS>SSC	FS>INS	SA>IS	SSI>IS	SNS>IS	SS>DS	SSC>SNS
DA>IS	IA>SSI	DS>DNS	DNS>SSC	IS>SSI	INS>SSI		SA>INS	SSI>INS	SNS>INS	SS>DNS	SSC>DS
DA>INS		DS>INS	DNS>SSI							SS>IS	SSC>DNS
DA>SSC		DS>IS								SS>INS	SSC>IS
DA>SSI		DS>SSC									SSC>INS
		DS>SSI									SSC>SSI

Unclear									
FA	FS>SA	FD	FI	SA>FS	SSI>SA	DNS>DS	IS>DA	FD>SSC	FI>SSC
FA>SA	FS>SS	FD>SA	FI>SA	SA>SSC	SSI>SNS	DNS>IS	INS>DA	FD>SSI	FI>SSI
FA>DA	FS>SNS	FD>DA	FI>DA	SA>SSI	SSI>SSC	DNS>INS	IS>DS		
FA>IA	FS>SSC	FD>IA	FI>IA	IA>DA	SNS>FS		IS>DNS		
FA>SS	FS>SSI	FD>FS	FI>FS	IA>DNS	SNS>SS		IS>INS		
FA>SNS		FD>FI	FI>FD	IA>DS	SNS>SSC		INS>DA		
FA>DS		FD>SS	FI>SS		SNS>SSI		INS>DS		
FA>DNS		FD>SNS	FI>SNS				INS>DNS		
FA>IS		FD>DS	FI>DS				INS>IS		
FA>INS		FD>DNS	FI>DNS						
FA>SSC		FD>IS	FI>IS						
FA>SSI		FD>INS	FI>INS						

Note. Table summarises the division of all contrasts into either response execution, proactive inhibitory, reactive inhibitory or unclear categories. **FA**=all fixations; **FS**=fixations presented in the SST; **FD**=fixations presented in the DT; **FI**=fixations presented in the IT; **SA**=all signal and no-signal trials in the SST, **DA**=all signal and no-signal trials in the DT; **IA**=all signal and no-signal trials in the IT; **SS**= signal trials in the SST; **DS**= signal trials in the DT; **IS**= signal trials in the IT; **SNS**=no-signal trials in the SST; **DNS**=no-signal trials in the DT; **INS**=no-signal trials in the IT, **SSC**=successful stop signal trials, **SSI**= unsuccessful stop signal trials. Contrasts are colour-coded per task context: green=DT, blue=IT, pink=SST, grey=no particular category.

Subsequent analyses were aimed at exploring (1) the consistency between the patterns of activity across subcortical ROIs and the pathways models; (2) the lateralised distribution of activity across ROIs; and (3) the interrelations of activity amongst regions under conditions of response execution and response inhibition[59] (Figure 3.3). Specific statistical analyses and results pertaining to each of these aims are outlined below. Both conventional null hypothesis testing and Bayesian statistics are reported throughout.

It should be indicated here that the approach to explore the interrelations amongst regions is based on conventional moderator/mediator analyses (Baron & Kenny, 1986; Judd, Kenny, & McClelland, 2001). This approach offers a simpler alternative (with fewer assumptions) to modelling approaches, such as Dynamic Causal Modelling and Psychophysical Interactions (Friston, Buechel, Fink *et al.*, 1997; Friston, Harrison, & Penny, 2003). The approach follows on neatly from initial ANOVAs (outlined below) and was deemed the cleanest way to unpack the differences across structures and conditions.

3.2.2.1. Pathway modelling analyses

For each BG structure, activity in each pathway is dependent upon the neuronal excitatory and inhibitory input they receive under the different behavioural conditions (Albin *et al.*, 1989, Alexander & Crutcher, 1990; Nambu *et al.*, 2002), leading to increases and decreases in activity which are represented by the models (see Figure 3.1). As mentioned above, here I make the assumption that changes in neural excitation and

[59] It should be noted that the analyses pertaining to aim (1) can be carried out independently of those employed to meet aims (2) and (3). Essentially these provide different approaches to exploring the pattern of activity under different response control conditions and their relation to predictions that can be made by the pathways models.

inhibition are met with corresponding increased and decreased BOLD activity (although I note, this is a contencious issue; e.g. Logothetis, 2008; Lauritzen *et al.,* 2012). These activations and deactivations can be described in a model as a series of positive (+1) and negative (-1) inputs, which can then be multiplied by the %BOLD averaged across all contrasts within a category (see Table 3.9). If the BOLD pattern conforms to the model, the values of the resulting variables will be greater than 0. However, if data is inconsistent with the model, the values of the resulting variables will be less than or equal to 0. The correspondence between the data and the model was assessed with one-tailed t-tests (as the hypothesis was directional) and complimentary Bayesian tests. For these analyses only, the Bayesian tests used the model as the basis of its prior which is represented by a uniform distribution (Dienes, 2008), limited to the absolute sum of %BOLD across ROIs. That is, the prior represents the pattern of the data that would be expected if the %BOLD perfectly conformed to the model. The limit of the prior was determined by the theoretical maximum extent to which the data could conform to the model. For completeness, analyses were also repeated using the JZS prior (see Table 3.9). The results of the application of the model to the data are summarised in Table 3.10. Note, that here, in accordance with the original pathways descriptions (Albin *et al.,* 1989; Alexander & Crutcher, 1990; Nambu *et al., 2*002), no assumptions were made with regards to the lateralisation of activity and thus %BOLD was extracted from bilateral structures.

Table 3.9. Modelling approach for each anatomical structure and the corresponding pathway.

Pathway	STR	GPe	GPi	STN	SN	THAL
Direct	+1	0	-1	0	-1	+1
Indirect	+1	-1	+1	+1	+1	-1
Hyperdirect	0	0	+1	+1	+1	-1

Note. **STR**= striatum, **GPe=** globus pallidus externa, **GPi**= globus pallidus interna, **STN**= subthalamic nucleus, **SN**= substantia nigra, **THAL**= thalamus, **+1**=upregulation of activity, **-1**=downregulation of activity, **0**=no involvement of structure.

The pattern of activity across ROIs within each category (i.e. response execution, proactive inhibition, reactive inhibition or all inhibition) were generally consistent with the model predictions (Table 3.10; Albin *et al.,* 1989, Alexander &

Crutcher, 1990; Nambu *et al., 2*002) and conformed to the pattern of activations and deactivations described in Figure 3.1. The resultant BFs computed using the informed prior are larger than those computed using the JZS prior (i.e. BF values vs. JZS values, Table 3.10), with the former indicating greater consistency between the data and the pathways models than the latter. Given the informed prior uses the pathways models themeselves as its basis, this prior contains more information about the distribution of activity within ROIs under different response control conditions, and thus is likely a closer reflection of the hypotheses than that provided by the JZS prior. As such, the resultant BFs may reveal more about the consistency of the data with the model than those BFs computed using the JZS prior. To confirm the reliability of the modelling approach the compound contrast data was applied to the inappropriate pathways (e.g. direct pathway × data based on response inhibition contrasts). These analyses found no support for a correspondence, substantiating the current approach (all B<0.099, Table 3.11).

Table 3.10. Summary of one-tailed t-tests and Bayesian equivalents of the fit between %BOLD averaged across each category for each ROI and the models used to represent each pathway.

Pathway		**t**	**df**	***p***	**BF**	**JZS**
Direct		2.13	29	.021	2.06	1.38
Indirect	Proactive	2.29	29	.015	2.7	1.83
	Reactive	3.4	29	<.001	57.05	18.08
	All	3.36	29	<.001	52.53	16.46
Hyperdirect	Proactive	2.25	29	.016	3.61	1.7
	Reactive	3.45	29	<.001	91.92	20.4
	All	3.29	29	<.001	59.74	14.31

Note. Contrasts categorised as response execution were applied to the direct pathways and contrasts categorised as response inhibition were applied to the indirect and hyperdirect pathways. **Proactive**= contrasts categorised as proactive inhibition; **Reactive**= contrasts categorised as reactive inhibition; **All**= all contrasts categorised as inhibition (including both proactive and reactive contrasts); **t**=t-value, **df**= degrees of freedom, **BF**=Bayes Factor calculated using a uniform prior, **JZS**= BF calculated using the JZS prior.

Table 3.11. Summary of one-tailed t-tests and Bayesian equivalents of the fit between %BOLD averaged across each category for each ROI and the inappropriate models.

Pathway	t	df	*p*	BF	JZS
Direct	-0.01	29	.502	0.1	0.19
Indirect	-1.12	29	.864	0.04	0.34
Hyperdirect	-0.76	29	.773	0.09	0.25

Note. Contrasts categorised as response execution were applied to the indirect and hyperdirect pathways and contrasts categorised as response inhibition were applied to the direct pathway. **t**= t-value; **df**= degrees of freedom; ***p***= *p*-value; **BF**= Bayes factor calculated using a uniform prior; **JZS**= Bayes factor calculated using the JZS prior.

3.2.2.2. The lateralised distribution of activity across regions of interest

Here I report analyses aimed at exploring the lateralised distribution of activity across cortical and subcortical ROIs. An initial 3-way ANOVA of condition (execution vs. inhibition), site (8 levels, each subcortical and cortical ROI), and hemisphere (left vs. right) as factors was applied to the raw %BOLD. The presence of a 3-way interaction between all factors ($F_{(7,203)}$=12.6, p<.001) indicate that right and left ROIs are recruited differentially under conditions of response execution and response inhibition. Importantly, a significant interaction between condition and hemisphere ($F_{(1,29)}$=54.47, p<.001) demonstrates that left hemisphere ROIs were recruited to a significantly greater extent than right hemisphere ROIs under conditions of response execution, and that right hemisphere ROIs were recruited to a significantly greater extent than left hemisphere ROIs under conditions of response inhibition relative to response execution (Figure 3.4)[60]. Subsequent simple effects analyses supported this lateralised pattern of activity (Table 3.12 and Figure 3.5) within specific ROIs. Under conditions of response execution, there was substantial evidence for involvement of left-lateralised subcortical dominance with pronounced associated activity in the left STR, GPe and THAL. Given that all responses were executed with the right hand this may be expected (Solodkin *et al.*, 2001). This pattern is consistent with descriptions of the pathways, where cortical input is received by the STR which feeds information forwards through thalamico-cortical projections (Albin *et al., 1*989, Alexander & Crutcher, 1990). Additionally

[60] The 3-way ANOVA also revealed significant main effects of hemisphere (right activity greater than left, $F_{(1,29)}$=34.5, p<.001), site ($F_{(7,203)}$=6.05, p<.001), and condition ($F_{(1,29)}$=7.56, p<.001). Significant interaction effects were also identified between hemisphere and ROI ($F_{(7,203)}$=40.2, p<.001), ROI and condition ($F_{(7,203)}$=11.92, p<.001).

bilateral IFG regions appeared to be activated during response execution. When responses were inhibited all anticipated ROIs (with the exception of the GPi) within the right hemisphere provided substantial evidence for a change in activity (see Table 3.12). In the cortex, only the right IFG and right pre-SMA exhibited response-inhibition-dependent responses.

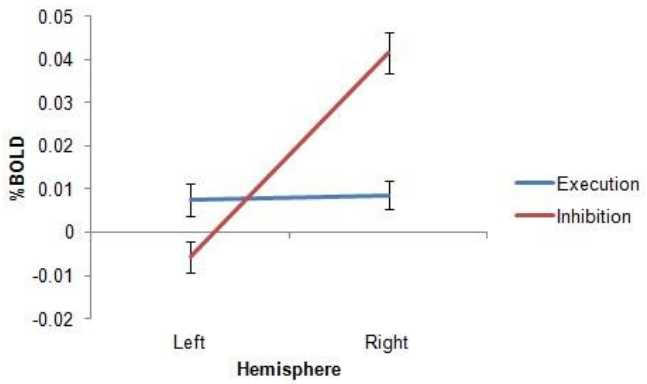


Figure 3.4. The interaction between hemisphere (left vs. right lateralised ROIs) and condition (response execution (blue line) vs. response inhibition (red line)) on %BOLD as revealed by repeated measures ANOVA. Error bars= ±1 within subject standard error (Cousineau, 2005; with correction, Morey, 2008).

The regions which demonstrated substantive differences when the response execution and response inhibition compound contrasts were applied were predominantly right lateralised; including the right SN, STN and THAL (see Table 3.12), suggesting that these regions may be critical in the difference between conditions - that is when response execution is blocked. Both bilateral regions of the IFG expressed such a difference between conditions whereas only the right pre-SMA did so.

Table 3.12. Simple effects analyses exploring the spatial distribution of cortical and subcortical activity under different response conditions.

		Execution vs. Inhibition			Execution			Inhibition		
Hem	ROI	t	*p*	BF	t	*p*	BF	t	*p*	BF
Left	pre-SMA	0.42	.676	0.21	1.24	.225	0.39	0.75	.458	0.25
	IFG	**-2.7**	.011	**4.03**	**-4.34**	<.001	**171.52**	0.68	.504	0.24
	STR	1.96	.059	1.04	**4.18**	<.001	**114.38**	1.07	.293	0.33
	GPe	1.26	.219	0.4	**3.21**	.003	**11.97**	1.77	.087	0.78
	GPi	-0.08	.935	0.2	1.08	.289	0.33	1.33	.194	0.43
	SN	-0.48	.638	0.22	1.23	.228	0.39	1.93	.063	0.99
	STN	-1.05	.302	0.32	0.11	.917	0.2	1.99	.056	1.09
	THAL	1.24	.224	0.39	**2.7**	.010	**4.62**	0.582	.565	0.23
Right	pre-SMA	-5.27	<.001	1788.11	-0.81	.425	0.26	**7.19**	<.001	**225367.62**
	IFG	-8.1	<.001	2026779.29	**-4.2**	<.001	**121.55**	**8.57**	<.001	**6062157.94**
	STR	-1.72	.096	0.72	2.09	.045	1.3	**4.49**	<.001	**248.98**
	GPe	-0.55	.59	0.22	**2.37**	.024	2.13	**3.58**	<.001	**27.54**
	GPi	0.003	.998	0.19	0.56	.578	0.23	0.56	.581	0.22
	SN	**-3.4**	.002	**18.03**	-1.64	.112	0.64	**4.52**	<.001	**269.46**
	STN	**-3.2**	.003	**11.69**	-1.42	.167	0.48	**4.43**	<.001	**215.75**
	THAL	**-3.34**	.002	**15.78**	-0.81	.424	0.26	**4.96**	<.001	**805.65**

Note**.** Summary of the simple main effects analyses for each region of interest when activity is compared between response execution and inhibition and under response execution and response inhibition conditions only. **Hem**=hemisphere; **ROI**= region of interest; **t**=t-value, significant t-values reported in bold; ***p***=*p*-value; **BF**=Bayes Factor, BFs>3 are reported in bold; **pre-SMA**=pre-supplementary motor area; **IFG**=inferior frontal gyrus; **STR**=striatum; **GPe**=globus pallidus externa; **GPi**=globus pallidus interna; **STN**=subthalamic nucleus; **SN**=substantia nigra; **THAL**=thalamus. All degrees of freedom=29.

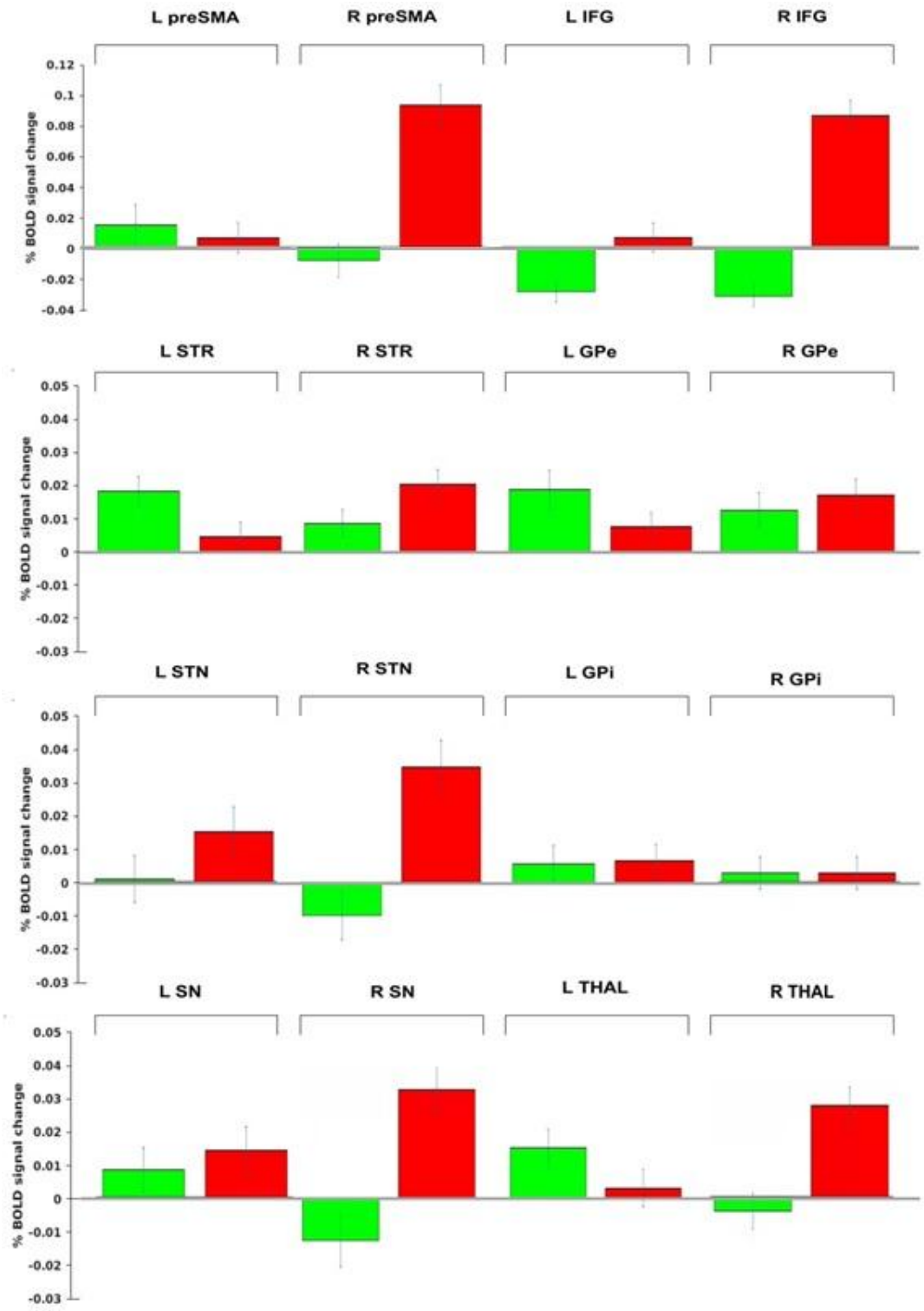


Figure 3.5. The change in %BOLD under conditions of response execution (green) and response inhibition (red) in left (**L**) and right (**R**) ROIs. The general trend of activity is suggestive of increased recruitment of right ROIs under conditions of response inhibition relative to response execution. **pre-SMA**= pre-supplementary motor area; **IFG**= inferior frontal gyrus; **STR**= striatum; **GPe**= globus pallidus externa; **STN**=subthalamic nucleus; **SN**=substantia nigra; **GPi**= globus pallidus interna; **THAL**= thalamus. Error bars are ± 1 standard error.

3.2.2.3. Interrelations between regions of interest

The preceding analyses demonstrate intriguing patterns in the data, but are silent as to the interrelationships between constituent structures. The simplest way to test for relationships between structures was to apply a series of moderator and mediator analyses (Baron & Kenny, 1986; Judd, Kenny, & McClelland, 2001) which were appended by Bayesian equivalents. To be eligible for moderator/mediator analyses, there must be a significant relationship between the variables of interest. A third variable can be considered a potential covariate if it correlates with the dependent variable. In Frequentist statistics a covariate has a mediating influence on the relationship between two other variables if its incorporation eliminates the significance of the original relationship. If this significant relationship is reduced but not eliminated, the covariate can be described as having moderating influence on the original relationship. Here %BOLD in ROIs in the same behavioural condition were included as covariates in analyses describing original differences in the data. Only those regions that showed a difference from baseline were included in these analyses (see Tables 3.12 – 3.14 and Figures 3.5 and 3.6).

During response execution, these analyses revealed that all significant subcortical activity within the left hemisphere appeared to be driven by activity within the STR. That is, addition of the STR as a covariate abolished the significant effects and the BF describing activity within the left GPe and THAL reduced from greater than 3 to less than 1/3. The addition of the left GPe and THAL as covariates did not reduce the BF corresponding to the left STR in a similar fashion, implying a directional relationship from left STR to GPe and THAL in-line with motor physiology (Figures 3.1 and 3.6; Albin *et al., 1*989, Alexander & Crutcher, 1990; Nambu *et al., 2*002). The left GPe also appeared to have a directional mediating effect upon the left THAL. This functional interplay is in keeping with the hypothesis that the STR receives cortical input, which is then directed towards the THAL, via the GPe (although note, the GPe is not conceptualised in the direct pathway Albin *et al., 1*989, Alexander & Crutcher, 1990). Both left and right IFG appeared to respond during response execution and correlated with one another. However there was no evidence for this activity influencing the subcortical structures, as the addition of the IFG regions as covariates had minimal effects upon subcortical activity.

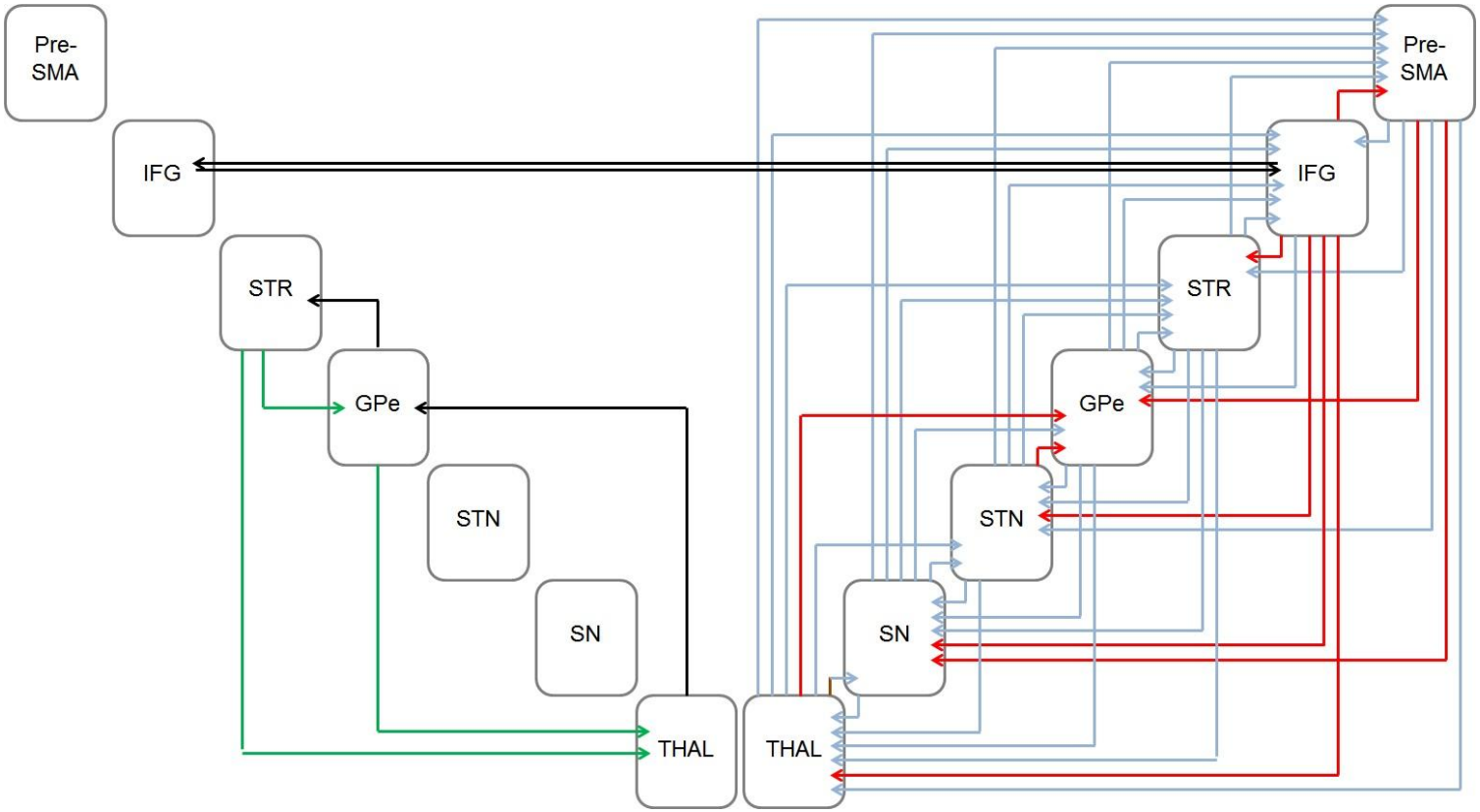


Figure 3.6. Schematic of the functional interrelations between the BG and THAL under conditions of response execution and response inhibition as revealed by moderator/mediator analyses based on the results from the Bayesian analyses. The direction of the relationship is shown by the arrows. Green and black arrows refer to response execution, with moderating relationships depicted in black and mediating relationships in green. Red and blue arrows refer to response inhibition conditions, with moderating relationships depicted in blue and mediating relationships in red. **Pre-SMA**=pre supplementary motor area; **IFG**=inferior frontal gyrus; **STR**=striatum; **GPe**=globus pallidus externa; **STN**=subthalamic nucleus; **SN**=substantia nigra; **THAL**=thalamus. Note that neither the left or right globus pallidus interna were included in the moderator/mediator analyses as the corresponding %BOLD was not found to be significant from 0 under conditions of response execution or response inhibition (Table 3.12)

Table 3.13. Summary of moderator/mediator analyses for activity under conditions of response execution.

			Left				Right		
Hem	ROI	Original	IFG	STR	GPe	THAL	IFG	STR	GPe
Left	IFG	<.001		<.001	<.001	<.001	.088	<.001	<.001
		171.520		**3.95E+03**	**2.45E+03**	**5.20E+03**	**0.78**	**N/A**	**N/A**
	STR	<.001	<.001		.030	.009	<.001	<.001	.004
		114.377	**2.67E+03**		**1.82**	**4.85**	**232.66**	**N/A**	**N/A**
	GPe	.003	<.001	.713		.113	<.001	.034	.048
		11.970	**185.61**	**0.21**		**0.65**	**112.93**	**N/A**	**N/A**
	THAL	.010	<.001	.601	.444		<.001	.105	.114
		4.618	156.01	.23	.26		35.59	N/A	N/A
Right	IFG	<.001	.136	<.001	<.001	<.001		<.001	<.001
		121.546	**0.56**	**246.73**	**1.06E+03**	**842.88**		**N/A**	**N/A**
	STR	.045					.004		.533
		N/A					**N/A**		**N/A**
	GPe	.025	.008	.764	.520	.335	.005	.237	
		N/A	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	

Note. BFs are shown in bold below the corresponding *p*-value. The original values correspond to those yielded from the simple effects analysis (Table 3.12). The table can be read from left to right, where the regions of interest (**ROI**) in each column correspond to the covariate added to the moderator/mediator analyses. **N/A**= no corresponding BF as criteria of BF>3 not met in the simple effects analyses (Table 3.12) and thus do not meet the criteria for exploration by moderator/mediator analysis (Baron & Kenny, 1986; Judd *et al.,* 2001). **IFG**=inferior frontal gyrus; **STR**=striatum; **GPe**= globus pallidus externa; **THAL**= thalamus. Values highlighted in blue represent instances of moderation. Values highlighted in orange represent instances of mediation. A covariate has a mediating influence on the relationship between two other variables if its incorporation eliminates the significance of the original relationship. If this significant relationship is reduced but not eliminated, the covariate can be described as having moderating influence on the original relationship.

Table 3.14. Summary of moderator/mediator analyses for activity under conditions of response inhibition.

	Original	pre-SMA	IFG	STR	GPe	SN	STN	THAL
pre-SMA	<.001		.285	<.001	<.001	<.001	<.001	<.001
	225367.617		**0.34**	**410.89**	**1485.5**	**147.67**	**376.22**	**96.23**
IFG	<.001	.006		<.001	<.001	<.001	<.001	<.001
	6062157.94	**7.56**		**3520.9**	**83642**	**2788.6**	**3415.1**	**1571.2**
STR	<.001	.119	.553		.035	.063	.108	.271
	248.980961	**0.62**	**0.23**		**1.61**	**1.02**	**0.67**	**0.35**
GPe	<.001	.409	.115	.960		.200	.349	.623
	27.5388707	**0.27**	**0.64**	**0.2**		**0.43**	**0.3**	**0.22**
SN	<.001	.501	.871	.057	.013		.184	.123
	269.456545	**0.24**	**0.2**	**1.09**	**3.78**		**0.46**	**0.61**
STN	<.001	.162	.989	.129	.025	.250		.237
	215.745656	**0.5**	**0.2**	**0.59**	**2.13**	**0.37**		**0.38**
THAL	<.001	.185	.309	.059	.008	.032	.044	
	805.649359	**0.45**	**0.32**	**1.07**	**5.55**	**1.72**	**1.34**	

Note. All ROISs are within the right hemisphere (see Table 3.12). BFs are shown in bold below the corresponding *p*-value. The original values correspond to those yielded from the simple effects analysis (Table 3.12). The table can be read from left to right, where the regions of interest (**ROI**) in each column correspond to the covariate added to the moderator/mediator analyses. **pre-SMA**= pre-supplementary motor area; **IFG**=inferior frontal gyrus; **STR**=striatum; **GPe**= globus pallidus externa; **SN=** substantia nigra; **STN=** subthalamic nucleus; **THAL**= thalamus. Values highlighted in blue represent instances of moderation, values highlighted in orange represent instances of mediation. A covariate has a mediating influence on the relationship between two other variables if its incorporation eliminates the significance of the original relationship. If this significant relationship is reduced but not eliminated, the covariate can be described as having moderating influence on the original relationship.

The spatial distribution of subcortical regions activated under response inhibition requirements were right-lateralised (Figure 3.5 and 3.6 and Table 3.14). These regions displayed a level of mutual interdependency where the addition of most ROIs as a covariate eliminated the significant status of other activations and reduced the corresponding BFs (and *p*-values). The right GPe proved an exception: the addition of other structures as a covariate reduced the right GPe BF (and *p*-value), while the addition of the right GPe as a covariate itself did not eliminate the presence of evidence in favour of response inhibition dependent activity in the other structures. This possibly suggests that the right GPe activation may be driven by the other regions; nevertheless, it exerts little influence upon other regions under response-inhibition conditions.

Analysis of response inhibition contrasts revealed the addition of the rIFG and right pre-SMA eliminated the significant status of all the observed subcortical response inhibition dependent activity. The reverse was not true: substantive evidence for inhibition dependent activity with rIFG and pre-SMA was present when other sub-cortical structures were added as covariates. This suggests top-down directional influence. Directionality is also suggested by the interplay between the rIFG and right pre-SMA, where the addition of the pre-SMA did not eliminate the significant status of the IFG, but the addition of the IFG did eliminate the changes in the pre-SMA. However, the effect size associated with rIFG is likely to have prevented complete mediation by the pre-SMA (Table 3.14 and Figure 3.5). Evidenced by the large reduction in BFs, the pre-SMA is also highly influential in modifying rIFG activity.

To summarise, these results largely corroborate the pathways models. Exploration of the spatial distribution of activity established lateralisation with respect to response control requirements. While left-hemisphere dominance was observed under conditions of response execution, right-hemisphere dominance was apparent under conditions of response inhibition. Furthermore, examination of the interrelations between regions revealed the direction of communication amongst BG ROIs under different action updating conditions. In the structures under investigation, activity within the left hemisphere appeared to be primarily driven by STR activity, whilst right hemisphere activity was largely driven by the rIFG and right pre-SMA (with mutual interdependence between subcortical regions). Collectively, these analyses reveal subcortical activity in accord with the putative pathways and provide insights into the direction of information flow under different conditions.

3.3. Discussion

The exploratory analyses outlined in this chapter aimed to establish how well the pattern of data within cortical and subcortial loci, as obtained in Study 1, conformed to the pathways models of response execution and response inhibition (Albin *et al.*, 1989; Alexander & Crutcher, 1990; Nambu *et al.*, 2002). The analyses largely corroborate the classic descriptions of the pathways (Albin *et al.*, 1989; Alexander & Crutcher, 1990; Nambu *et al.*, 2002). The novel compound contrast method provided data that converged with expectations and expanded upon them through the demonstration of lateralised patterns of activity. These findings suggest a mechanism in which response execution is implemented by a left-hemispheric network, which is then actively blocked by a right-lateralised inhibitory network. This proposition is in agreement with, and extends, models of left hemisphere dominance in the acquisition of new motor skills and sequences, and the right hemisphere for the amendment of ongoing action plans (Mutha, Haaland, & Sainburg, 2012). In this instance right hemisphere dominance is associated with the requirement to inhibit, as opposed to add to, ongoing responses.

Existing theory proposes that the STR is the first sub-cortical structure to receive cortical input before transmission downstream in the *direct* and *indirect* pathways (Albin *et al.*, 1989, Alexander & Crutcher, 1990; Nambu *et al.*, 2002). This role is consistent with the observation here that the STR influences activity in other ROIs when either a response was to be made or cancelled. Specifically, under conditions of response execution, the addition of the left STR as a covariate eliminated response execution effects observed within the left GPe and left THAL, but neither the left GPe or the left THAL appeared to demonstrate mediating influence over the left STR; indicating the direction of strongest influence was from the left STR (see Figure 3.5 and 3.6, also Table 3.13). The activation of the left GPe during response execution is not obviously supported by the original descriptions of the direct and indirect pathways (Figure 3.1; Albin *et al.*, 1989, Alexander & Crutcher, 1990) and the results indicate that the GPe may play a more crucial role in action-updating than originally conceived. Consistent with this, recent work in rats has established the presence of direct projections between the GPe and the frontal cortex (Chen, Ferrari, Sacchet *et al.*, 2015; Saunders, Oldenburg, Berezovskii, *et al.*, 2015; Milardi, Gaeta, Marino *et al.*, 2014), as well as the activation of GABAergic projections from the GPe to the STR under stop relative to go conditions (Mallet *et al.*, 2016). Specifically, it has been suggested that

the GPe may play a role in the execution of response sequences (Chan, Surmeier, & Yung, 2006; see also Nambu, 2008), which is required on signal trials in the DT (i.e. by the requirement to execute an initial response using either the index or middle finger, followed by a thumb response).

The directionality and lateralisation of subcortical activity can be extended to the cortex where under conditions of response inhibition BG and THAL activity were driven by the rIFG and the right pre-SMA. The rIFG was found to influence activity within the pre-SMA[61] and is consistent with recent work by others (Jahfari *et al.*, 2011, 2012; Rae *et al., 2*015; Duann *et al., 2*009), particularly that of Rae *et al.* (2015) who established the rIFG was responsible for modulating excitatory connectivity between the pre-SMA and STN under conditions of successful response inhibition. These results therefore further corroborate the effective connectivity between cortical and subcortical regions when the cancellation of actions is required.

Under conditions of response inhibition, right structures were recruited as predicted by the *indirect* pathway with the exception of the GPi (potentially owing to the small BOLD effects established under all conditions in both hemispheres; Figure 3.5, Table 3.12 and Table 3.13). The subcortical loci activated under requirements of response inhibition appeared to be highly inter-correlated but driven by the rIFG and the right pre-SMA. Speculatively, the interdependency between subcortical structures may be the result of continual feedback loops between regions, ensuring cancellation of motor plans when presented with a stop signal. Such possibilities are evidenced by extensive interconnectivity between activated regions observed in previous work (Blakemore & Choudhury, 2006; Chan *et al*., 2006; Graybiel, 2005; Nambu, 2008; Smith, Raju, Pare, & Sidibe, 2004). Importantly, when action plans were cancelled, the demonstrable activity in the right GPe was found to be eliminated when activity in all of the other regions was taken into account. However, the GPe appeared to exert minimal influence itself. This, together with the relatively small effect size present in the right GPe (Figure 3.5) is consistent with the hypothesis that the GPe is bypassed in the hyperdirect pathway and therefore evidences the existence of this rapid route for implementing response inhibition (Nambu *et al., 2*002; Aron & Poldrack, 2006; Aron *et al., 2*007).

[61] The rIFG had a very large effect size which may have prevented complete mediation by the pre-SMA (Figure 3.3).

This interpretation may also help to explain why bilateral GPe and right STR activity was found to be increased in participants with long relative to short SSRTs. To speculate, participants who are more efficient at stopping (i.e. have short SSRTs) may be more likely to implement response inhibition via the hyperdirect pathway, thus bypassing these structures. Conversely, since participants with longer SSRTs are expected to be less efficient at implementing response inhibition, they may be more likely to recruit the slower, indirect route in order to successfully countermand responses.

The relationship between left STN activity and DRT2 is difficult to interpret. Left STN was found to be associated with greater activity in participants with short relative to long DRT2s. The STN itself is hypothesised to be bypassed under conditions of response execution and actually increased when responses are to be cancelled (Albin *et al., 1*989; Alexander & Crutcher, 1990; Nambu *et al., 2*002). Furthermore, the left STN was not found to be substantially activated under conditions of response execution via the pathways analyses. Thus it is possible that this may well be a spurious finding and further work may be required to assess the replicability of this result.

The indirect and hyperdirect pathways are theorised to block thalamico-cortical output (Albin *et al., 1*989; Alexander & Crutcher, 1990; Nambu *et al., 2*002; Aron & Poldrack, 2006; Aron *et al., 2*007). As such we anticipated a decrease in BOLD response within the THAL to reflect a down-regulation during response inhibition. Conversely, the right THAL was recruited to a greater extent under conditions of response inhibition relative to response execution. Hypothetically, it is possible that the integration of the execution and inhibition processes required to block thalamico-cortical output is more energy demanding than those required to implement an existing action plan; hence metabolic activity is increased (Hershey *et al*., 2004; Logothetis, 2008)[62]. This may also occur at other nodes in the pathways which are hypothesised to react differently under conditions of response execution and response inhibition. Activity in the GPi and SN are theorised to be reduced under conditions of response execution and increased under conditions of response inhibition. It is therefore possible

[62] This interpretation also accounts for the increase in BOLD in bilateral THAL and GPe with SSRT (Table 3.1) when the pathay model predicts a decrease in neural activity within these ROIs when responses are to be inhibited (although note, BFs were towards the null/inconclusive for these analyses – BF=.23-.38 and .45-.98, respectively). Note also, that while the GPe is not considered a node crucial to the execution of a response in the original pathways model, the analyses presented here suggest otherwise (i.e. that it may play a role in feeding information forward from the left STR to the left THAL) and thus this region could exhibit increased BOLD activity as a result of opposing neural signals when a response is to be countermanded.

that an increase in activity within these regions occurs when opposing signals are integrated. This interpretation is consistent with the observations of SN activity (as activity was greater under conditions of response inhibition relative to response execution; see Table 3.12 and Figure 3.5). However, this does not explain the activity in the GPi as recruitment of this region did not different under conditions of response execution and response inhibition (Table 3.12), potentially owing to the small effect sizes observed (Figure 3.5). Importantly, the potential for the assimilation of opposing neural signals to increase BOLD highlights a major limitation to the modelling approach adopted in this chapter. As mentioned, these analyses assumed correspondence in the direction of BOLD signal and neuronal activation and deactivation. Although previous research has demonstrated this equivalence (e.g. Kastrup *et al.*, 2008; Schäfer *et al.*, 2012), the findings presented here, particularly in relation to the THAL, demonstrate this relationship may be dependent on the specific cognitive processes explored (see also Hershey, Revilla, Wernle *et al.* 2003).

The findings presented here also indicate a potential difference between proactive and reactive inhibition, in that greater consistency between the data and models were found for the hyperdirect (reactive) relative to the indirect (proactive) pathway (Table 3.10). This difference may be due to a rather trivial explanation, in that the detection of a signal and the active blocking of THAL output is more energy demanding (as noted above; Logothetis, 2008) leading to increased BOLD responses. This may also explain why the data provided greater consistency with the indirect pathway when all stop-related contrasts were considered rather than proactive only. However, in the SST proactive control tendencies are likely to be adopted on all trials (as participants are instructed that they *may* have to withhold their response on some trials), therefore distinct separation of these processes (and therefore pathways) within the framework of the SST is difficult (see also Jahfari et al.'s, 2011, 2012, hyper-indirect model).

It is noteworthy that functional lateralisation of motor control observed here may be associated with handedness. In the current study all participants were right-handed and previous work has identified contralateral activation of BG during hand movements (Solodkin et al., 2001). Although handedness does not cause lateralisation of function within the brain, common factors may underlie both hand dominance and functional organisation (McManus & Bryden, 1992; Mutha, Haaland, & Sainburg, 2012) and as such must be considered in interpreting the current work. In accord, the degeneration of

BG nuclei in Parkinson's Disease (PD) is associated with symptom onset in contralateral limbs (Pirker *et al., 2*003; Wu *et al.,* 2015) and handedness has been found to predict the most affected side of symptoms - which is most commonly the side of the dominant hand (Yust-Katz, Tesler, Treves, Melamed, & Djaldetti, 2008). Although the link between dominant hand and symptom presence is not known, it has been proposed to be associated with anatomy (Barrett, Wylie, Harrison & Wooten, 2013). This study therefore highlights the structural and functional asymmetries that underlie response control and encourage its exploration in movement disorders. fMRI may provide a useful technique in the investigation of such work.

Although fMRI as a technique has been criticised for its inability to detect small changes in BOLD responses (Chevrier *et al., 2*007) the approach outlined here enabled the delineation of the BG and THAL in the putative pathways and even suggested how they might be revised (with the addition of the GPe to the direct pathway; see also Nambu, 2008). This was likely assisted by the exclusion of physiological regressors (Bright & Murphy, 2013; Brooks *et al.,* 2013), and the incorporation of the novel compound contrast analyses; which is theoretically more robust than the common practice of choosing individual representative contrasts. Such methods could potentially be further developed to provide functional biomarkers of BG disorders, such as those in PD; enabling the exploration of the interrelations between cortical regions and BG nuclei in addition to the hyperactivity of the GP/STN most commonly identified (see Jahanshahi *et al.,* 2014 for a review).

These analyses are met with a number of limitations. Specifically, the similarity of patterns of activity in the SN and STN may be due to potential assimilation of BOLD activity between these regions. Although the same pattern of activity is hypothesised in both the indirect and hyperdirect pathways (Albin *et al., 1*989; Alexander & Crutcher, 1990; Nambu *et al., 2*002), the small size of these structures and the spatial resolution of fMRI imply mixing of signals between the STN and SN are possible (de Hollander, Keuken, & Forstmann, 2015). In addition, the use of a spatial smoothing kernel in these analyses is likely to have exacerbated this (de Hollander *et al., 2*015). However, the methods used here were pre-registered (https://osf.io/zbk3p/) and based on previous work (Aron & Poldrack, 2006; Aron *et al., 2*007), but exploration in the absence of a smoothing kernel should be considered in future work. In addition, manual

identification of the STN and SN may enhance reliability of interpretations[63], and scanning at higher field strengths (e.g. 7T or above) would facilitate identification and localisation of these regions (de Hollander *et al.,* 2015; Keuken *et al.,* 2014; Keuken, Bazin, Schäfer *et al.*, 2013) and may provide better accuracy for future work. Furthermore, the modelling approach adopted (Section 3.2.2.1) may not have been as thorough as it could have been. Specifically, the approach used here treat the BOLD activity extracted from each ROI with equal importance as the specific contribution to pathways provided by each is unknown. However, the reliability of the BOLD signal is known to differ with the size and location of the ROI from which it is extracted (Friedman, Stern, Brown *et al.*, 2008; Plichta, Schwartz, Grimm *et al.*, 2012), and could be taken into account in future work. For example, %BOLD could be weighted according to the number of voxels comprising the ROI.

In conclusion, the results presented here demonstrate that it is possible to detect functionally distinct response control pathways under different action updating conditions. Crucially, not only was the existence of the pathways largely confirmed, these findings extend previous proposals of motor laterality in the human brain. The work here is exploratory and replication and confirmation are required, but could potentially open avenues for future work and development of the use of fMRI in the exploration of the role of the BG in action control.

[63] Although the use of probability atlases, such as the ATAG used here, are also recommended (de Hollander *et al., 2*015).

Chapter 4. Study 2, Part I

The neurophysiology and neurochemistry of action updating in human prefrontal cortex: A combined TMS/MRS/fMRI study

4.1. Introduction

The principal inhibitory neurotransmitter, GABA, has been argued to be crucial for motor learning (Floyer-Lea *et al.*, 2006; Stagg, Bachtiar, & Johansen-Berg, 2011) and recent work has highlighted its potential role in both the waiting and stopping of actions (see Hayes *et al.*, 2014, for a recent review). In general, studies have found increased GABA concentration to be related to better inhibitory control, including elevated performance on tasks requiring the withholding of actions and the suppression of distracting information (Boy *et al.*, 2010, 2011; Silveri *et al.*, 2013; Sumner, Edden, Bompas *et al.*, 2010; Quetscher *et al.*, 2014) . Furthermore, atypical levels have been found in patients with conditions for which behavioural deficits include impaired response control (e.g. patients with schizophrenia, PD and ADHD; Hall, Prokic, McAllister *et al.*, 2014; Nakazawa, Zsiros, Jiang *et al.*, 2012; Rivero, Selten, Sich *et al.*, 2015; see Schür, Draisma, Wijnen *et al.*, 2016, for a recent review of the role of GABA in psychiatric disorders). Increased GABA may confer better management of motor deficits in these patients (Draper *et al.*, 2014). As response inhibition refers to the suppression or cancellation of ongoing motor activity and GABA acts to suppress neuronal excitability, we cannot assume equivalence between the concepts (Aron, 2007). However, the evidence thus far suggests a possible link between behavioural and neurochemical inhibitory mechanisms that warrants further investigation. In addition, it is unclear whether GABA acts to support action updating processes more broadly. Here, I explore the role of GABA in both response inhibition and non-inhibitory action updating.

Positive relationships between GABA and motor response inhibition are not always found (e.g. Boy *et al.*, 2011; Deakin, Aitken, Dowson *et al.*, 2004; Lane, Tcheremissine, Lieving *et al.*, 2005) and may be due to the difficulty in modulating GABA concentration by behavioural means alone (Puts & Edden, 2012). Here, I attempt to enhance the potential for establishing a link between behavioural indices of

action updating and GABA by the application of continuous theta burst stimulation (cTBS) - an offline neurostimulation technique that has been found to increase cortical GABA concentration in motor, occipital and frontal regions (Allen, Dunkley, Muthumaraswamy *et al.*, 2014; Dubin, Mao, Gordon *et al.*, 2014; Stagg, Wylezinska, Matthews *et al.*, 2009, see Figure 4.1). At the same time, cTBS is known to reduce cortical excitability[64] (Huang *et al.*, 2005, 2011; Franca, Koch, Mochizuki *et al.*, 2006), and when applied to the rIFG has been found to impair both SST and DT performance (Verbruggen *et al., 2*010; see also Chambers *et al.*, 2006, 2007; Dambacher *et al.*, 2014). This provides additional opportunities to establish links between action updating and neurophysiology.

Here, I employed a novel combination of the context-cueing paradigm (Study 1; Verbruggen *et al., 2*010), cTBS, magnetic resonance spectroscopy (MRS; a technique that enables GABA quantification *in vivo*) and fMRI. I primarily aimed to establish whether modulation of GABA concentration, %BOLD and behaviour was possible via cTBS to the rIFG[65], thus replicating and extending the findings of Verbruggen *et al.* (2010). Crucially, I aimed to establish whether cTBS-modulation of GABA was related to cTBS-modulation of behaviour. If so, this would provide a link to the neurochemical basis of action updating. The possible relationships between measures at baseline and those induced by cTBS were explored as was the prospect of replicating the fMRI results from Study 1.

Given the multiple aims of the study, I provide an initial overview of the relevant literature and associated hypotheses. All aims, hypotheses, methods and statistical analyses were pre-registered under the Open Science Framework (https://osf.io/4z7pu/) prior to data collection.

[64] Although note, individual variability in response to cTBS has been reported (e.g. Hamada, Murase, Hasan *et al.*, 2013).

[65] Although Study 1 revealed common activation in posterior rIFG and pre-SMA for both inhibitory and non-inhibitory action updating demands, the rIFG was selected for the site of cTBS application here as previous work suggests the pre-SMA may be too deep in the medial wall to be influenced by cTBS (Verbruggen *et al., 2*010). Additionally, the rIFG may be more influential in action updating given activity within this region was found to mediate that in the pre-SMA and basal ganglia under response inhibition conditions.

4.2. Aims and hypotheses

To clarify, the primary aims of the study were to establish whether key dependent measures (RT to no-signal trials, SSRT, DRT2, GABA concentration and BOLD) were altered by the application of cTBS to the rIFG relative to control (sham) cTBS[66]. Such cTBS-induced changes in measures may provide a link between different mechanisms underlying action updating. Therefore I examined whether potential cTBS-induced modulation of the dependent measures were related via the computation of active – sham difference scores. Additionally, I was interested in (a) whether relationships between measures were present at baseline (i.e. those acquired subsequent to sham cTBS application only), (b) whether the effects of cTBS (if any) varied over time, (c) whether there was evidence for effects of cTBS on BOLD activity in regions remote to the cortical site of stimulation and (d) whether it was possible to replicate the pattern of activity under different conditions established in Study 1. Analysis and results relevant to the replication of fMRI data in Study 1 are reported in Chapter 5.

4.2.1. The effects of cTBS when applied to the rIFG

4.2.1.1. The effect of cTBS on GABA concentration

The mechanisms by which cTBS exerts its effects are unclear, but recent evidence suggests that it may be linked to GABA (e.g. Stagg *et al.*, 2009; see Huang *et al.*, 2011, for a discussion of the role of glutamine). GABA itself acts to hyperpolarise cells, reducing neuronal sensitivity to excitatory input (Isaacson & Scanziani, 2011). It is theorised that prolonged hyperpolarisation produces the long-term depression-like effects observed after cTBS application (Stagg, O'Shea, & Johansen-Berg, 2010). Consistent with this hypothesis, cTBS has been found to increase local GABA concentration when applied to motor and occipital regions (Stagg *et al.*, 2009; Allen *et al.*, 2014; Figure 4.1). Indirect increases in GABA in the ventromedial prefrontal cortex have also been found after application of cTBS to the DLPFC (Dubin *et al.*, 2014). However, such elevations in GABA subsequent to cTBS application are not always

[66] The term sham is used to describe the control condition for cTBS in which the TMS coil is orientated 90° away from the scalp (see Section 4.3.3.3.4.2 and Figure 4.7). This enables the auditory artefact associated with cTBS application to be maintained, whilst minimising the magnetic flux that reaches the cortex (Lisanby *et al.*, 2001).

found (e.g. Stagg *et al.*, 2009, found no such increase in GABA concentration after cTBS was applied to the vertex) and as such may be region-dependent. While Dubin *et al.*'s (2014) findings indicate the possibility that frontal GABA may be increased after cTBS, they do not report whether GABA concentration at the site of application was modulated by cTBS. Furthermore, Dubin *et al.*'s work involved clinically depressed patients for whom atypical GABAergic mechanisms have been proposed (Brambilla, Perez, Barale *et al.*, 2003; Cryan & Kaupmann, 2005; Petty, Kramer, & Hendrickse, 1993). As such, the anticipated relationship between cTBS and frontal GABA in healthy participants was unclear.

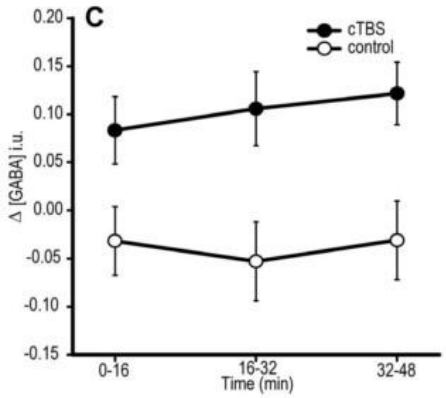


Figure 4.1. Modulation of occipital GABA concentration subsequent to application of cTBS to occipital cortex. Image from Allen *et al.* (2014). Change in GABA is represented as ΔGABA in institutional units relative to a pre-cTBS baseline. GABA concentration was found be elevated relative to control (sham) cTBS, but the effect was not found to be time-dependent.

4.2.1.2. The effect of cTBS on behaviour

As mentioned, the inclusion of the context-cueing paradigm with cTBS in the current study provided an opportunity to replicate the findings by Verbruggen *et al.* (2010). As outlined in Chapter 1 (Section 1.2.1.2), participants were found to be reliably impaired on both SST and DT performance (i.e. inhibitory and non-inhibitory processes, respectively) after application of cTBS to the rIFG. Crucially, this impairment was found only on signal trials across each of these tasks: RTs to no-signal trials were found to be reduced, as were RTs to the first response on signal trials in the DT (DRT1); corresponding to conditions where no action updating was required (Figure 4.2). Accordingly, I anticipated there to be an elongation (reflective of a disruption) of SSRT

and DRT2, with a decrease in RTs to no-signal trials after cTBS to the rIFG when compared with sham. Furthermore, I anticipated that any effects of cTBS on DRT2 would not differ over SOAs as found by Verbruggen *et al.* (2010)[67]. I planned to explore this further by establishing cTBS effects both within- and post-bottleneck (as per the quantification procedure outlined in Section 2.3.1) as well as across SOAs.

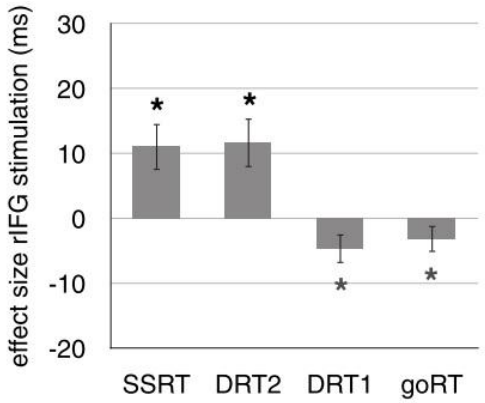


Figure 4.2. Key results from Verbruggen *et al.* (2010) showing modulation of reaction time (RT) performance in the SST and DT after cTBS to the rIFG. A slowing of the stop signal reaction time (SSRT) and double-response reaction time (DRT2) was observed, reflecting impairments in inhibitory and non-inhibitory action updating, respectively. This is in contrast to the decrease in RTs observed to no-signal trials (goRTs) and the initial response on double-signal trials (DRT1), where no updating of ongoing action plans was required.

4.2.1.3. The effect of cTBS on BOLD in the rIFG

When applied over the right frontal eye field, cTBS has been found to yield a reduction in BOLD activity of ~40% relative to baseline (Hubl, Nyffeler, Wurtz *et al.*, 2008). In frontal regions, hemodynamic changes in the form of reduced cerebral blood flow and oxygen have been found after application of cTBS to the right DLPFC (e.g. Tupak, Dresler, Badewien *et al.*, 2013). To my knowledge, the modulation of the BOLD response subsequent to cTBS over ventrolateral prefrontal cortex has not been tested, but I anticipated a reduction in BOLD following active compared to sham cTBS as per Hubl *et al.* (2008).

[67] To dissociate between attention and action-updating explanations, the authors considered their findings with respect to the Psychological Refractory Period (PRP; Telford, 1931; Welford. 1952; Pashler, 1994). Impairments in DRT2 were found not to differ across SOAs and as such the cTBS effects were argued not to differ between the pre- and post-bottleneck periods.

4.2.2. Relationships between measures

4.2.2.1. The relationship between GABA and behaviour

As outlined above previous work has typically found a positive relationship between GABA concentration and inhibitory control (e.g. Boy *et al.*, 2010; Silveri *et al.*, Sumner *et al.*, 2010; Quetscher *et al.*, 2014). Thus a negative correlation between SSRT (where shorter SSRTs are indicative of better inhibitory control) and rIFG GABA in the absence of cTBS might be expected. Conversely, Boy *et al.* (2011) failed to find a correlation between motor inhibition as measured by SST performance and GABA levels in the rIFG and DLPFC. However, it is possible that the null findings may have been associated with a small sample size (N=12), as well as limited variation amongst participants, which may be increased by the introduction of an intervention, such as cTBS.

Existing studies on the effects of cTBS on inhibitory control and GABA appear to produce contradictory results from what may be anticipated at baseline. GABA levels appear elevated after cTBS (e.g. Allen *et al.*, 2014; Dubin *et al.*, 2014; Stagg *et al.*, 2009), and a negative correlation between SSRT and GABA may be expected. However, SSRT has been found to be impaired after cTBS (Verbruggen *et al.*, 2010). As the evidence is unclear the following scenarios were possible: (1) If a general GABAergic mechanism underlies general action updating (inhibitory and non-inhibitory) I anticipated a comparable modulation of GABA with SSRT and DRT2. That is, if GABA was found to increase, I anticipated both SSRT and DRT2 to decrease. (2) If cTBS-induced changes in GABA were specifically related to response inhibition only, then I expected this relationship to occur only between the change in GABA concentration and the change in SSRT. (3) If a GABAergic mechanism underlies only *non*-inhibitory action updating and not response inhibition, then cTBS-induced changes in GABA concentration would be comparable to cTBS-induced changes in DRT2 and not SSRT. (4) If cTBS-induced changes in GABA were unrelated to those changes in SSRT and DRT2, this could indicate that the neural underpinning of action updating in prefrontal cortex is not GABAergic in nature[68].

[68]It was also possible that my methodological approach may be insensitive to detection of such relationships.

4.2.2.2. The relationship between BOLD and behaviour

Previous work has established a suppressive influence of cTBS on BOLD activity (Hubl *et al., 2*008) and prolonged SSRT and DRT2 in the context-cueing paradigm (Verbruggen *et al.,* 2010), relative to sham stimulation. Given that BOLD is argued to be an indirect measure of neuronal activity (e.g. Logothetis, Pauls, Augath *et al.*, 2001), and cTBS is argued to suppress neuronal activity (Huang *et al.,* 2005), it was anticipated that cTBS induced effects would be correlated. In support, Hubl *et al.* (2008) found cTBS-induced changes in a saccade task to be correlated with cTBS-induced changes in BOLD.

4.2.2.3. The relationship between BOLD and GABA

cTBS has been found to increase GABA concentration (Allen *et al.,* 2014; Dubin *et al.,* 2014; Stagg *et al.,* 2009) and reduce BOLD activity (Hubl *et al.,* 2008) and as such negative correlations between these measures subsequent to cTBS application to the rIFG were expected. BOLD activity is argued to be dependent on the excitatory-inhibitory balance between Glx (glutamate-glutamine) and GABA, respectively (Lauritzen *et al.,* 2012) and inverse relationships between GABA and BOLD have been found (see Duncan, Wiebking, & Northoff, 2014, for a review). However, positive correlations between BOLD and GABA have been observed in the insula (Wiebking, Duncan, Tiret *et al*., 2014) and DLPFC (Harris, Puts, Anderson *et al.*, 2015; note, this did not survive correction for multiple comparisons) and absence of relationships have been reported in other regions (e.g. Harris *et al.,* 2015 found no positive relationships between GABA and BOLD in multiple cortical site including occipital cortex, motor cortex, sensorimotor cortex and frontal eye field). The reasons for these discrepancies are unclear, but it is possible that BOLD-GABA relationships may be region dependent and/or a lack of statistical power may increase the likelihood of observed false positive and false negative findings (Harris *et al.,* 2015)[69].

[69] Here, it was anticipated that there be an inverse relationhip between GABA and BOLD within the rIFG, while above it was noted that elevated GABA might be related to better inhibitory control (i.e. GABA would be expected to negatively correlate with SSRT). Together these hypothesis indicate the potential for increased GABA to be associated with less BOLD but better inhibitory control. Such expectencies are at odds with previous work that has shown increased rIFG BOLD to be associated with better inbhibitory

4.2.3. Exploratory analyses

4.2.3.1. The time course of cTBS related effects

It is known that the suppressive effects of cTBS on neural activity take time to develop, with maximum effects typically found between 10 and 50 minutes after administration (Huang *et al.*, 2005; Figure 4.3). After this time, the effects of cTBS start to weaken as neuronal excitability returns to baseline. Time-dependent variation in cTBS-induced modulation of measures of action updating and BOLD have been demonstrated previously (Hubl *et al.*, 2008; Verbruggen *et al.*, 2010[70]), but such variation in occipital GABA concentrations have not (Allen *et al.*, 2014; Figure 4.1). This remains to be explored in prefrontal regions.

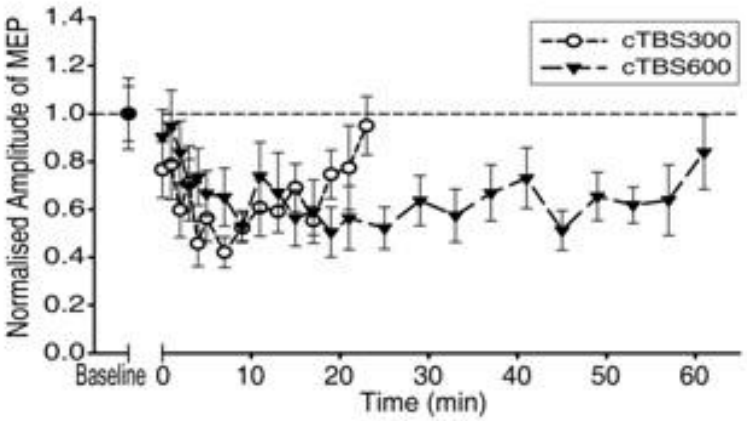


Figure 4.3. Image from Huang *et al.* (2005) depicting the suppressive effects of cTBS on the amplitude of motor evoked potentials (MEP) when applied to the human motor cortex. The amplitude of the MEPs was reduced for one hour relative to baseline (dashed line) after the application of 600 TMS pulses (cTBS600, filled inverted triangles).

4.2.3.2. The remote effects of cTBS on BOLD

Strong functional and anatomical connectivity between both cortical and subcortical regions involved in motor control are well established (e.g. Aron *et al.*, 2007; Duann *et*

control (negatively correlated with SSRT, Aron & Poldrack, 2006). However, I found no such relationship between %BOLD and SSRT in Study 1 (see Table 2.4).

[70] Although note there was much individual variability in response.

al., 2009; Forstmann *et al.*, 2010, *2*012; Jahfari et al., 2011, 2012) and results reported in Chapter 3 suggest the rIFG is involved in the mediation of both pre-SMA and subcortical activity (see also Rae *et al.*, 2015). As such, I was interested in establishing whether cTBS to the rIFG was able to modulate activity in remote sites of the response control network. Previous work has found effects of TMS distal to the site of application (Hubl *et al.*, *2*008; Siebner *et al.*, 2010; Volz, Hamada, Rothwell, & Grefkes, 2015), including the basal ganglia (Bestmann, Baudewig, Siebner *et al.*, 2004; Zandbelt *et al.*, 2013).

4.3. Methods

4.3.1. Study Design

A within-subject design was employed where active and sham (baseline) cTBS was administered to the rIFG prior to MRS and fMRI, whilst participants simultaneously performed a simplified version of the context-cueing paradigm employed in Study 1 (see also Verbruggen *et al.*, *2*010). Since it is not possible to acquire MRS and fMRI measurements simultaneously, I interleaved these acquisitions as a means to obtain data across separate time points (see Section 4.3.3.4). Participants completed the context-cueing paradigm during both MRS and fMRI acquisitions.

4.3.2. Participants

30 right-handed participants completed the study[71] (8 male, 22 female), aged between 19 and 32 years old (*M*=22.67, *SD*=3.11 years). Age range was restricted due to observed GABA- and vascular-related changed with increased age (Ajmani, Metter, Jaykumar *et al.*, 2015; Gao, Edden, Li *et al.*, 2013; Silveri *et al.*, 2013). Participants had normal or corrected-to-normal vision, were neurologically healthy and screened for medical contraindications to TMS and MRI. Participants were asked to abstain from

[71]The sample size was limited due to practical constraints. Sensitivity analyses were carried out in GPower 3.1.9.2. http://www.gpower.hhu.de/; Faul, Erfelder & Buckner, 2007; Faul, Erdfelder, Buchner, & Lang, 2009) to establish expected effect sizes. With α set to 0.05, 2-tailed t-tests estimates were dz=0.529 and dz=0.6124, at 80% and 90% power respectively. For 2-tailed bivariate correlations critical r values were 0.361 at both 80% and 90% power).

drug and alcohol use and to minimise caffeine consumption for a minimum of twelve hours prior to testing, to comply with TMS safety requirements (Maizey *et al.*, 2013 and APP2.1). Female participants completed additional screening (see Section 4.3.2.1). Informed consent was provided by each participant and all research was approved by the ethics committee at the School of Psychology, Cardiff University. Participants were reimbursed at a rate of £10 per hour for their time (total reimbursement was £135 per participant).

4.3.2.1. Additional screening for female participants

Female participants were additionally screened to establish whether they had naturally occurring or hormonally controlled menstrual cycles. Previous work has established elevated GABA concentrations during the ovulatory and follicular phases relative to the luteal phase in females with naturally occurring cycles (De Bondt, De Belder, Vanhevel, *et al.*, 2014; Epperson, Haga, Mason *et al.*, 2002; Harada, Kubo, Nose *et al.*, 2011)[72]. However, such fluctuations in prefrontal GABA do not occur in females with hormonally controlled cycles (De Bont *et al.*, 2014). As such, MRS acquisitions for those participants using hormone-based contraceptives were obtained at any phase of the menstrual cycle. MRS acquisitions for females with naturally occurring cycles were limited to the luteal phase. The onset of the luteal phase was estimated using the forward cycle technique (Udry & Morris, 1977). This technique considers the first day of the menstrual cycle as the first day of menstrual bleeding, and then splits the various phases according to the four weeks of the average twenty-eight day cycle (Wilcox, Dunson, & Baird, 2000). Weeks one and four were considered the luteal phase, and weeks two and three considered the follicular and ovulatory phases. An example of the screening form used is provided in APP10.3.1.

[72] Fluctuations in response inhibition capabilities (as measured via the SST) have also been identified in females across the menstrual cycle, with less efficient abilities, relative to male participants, in the follicular phase (Colzato, Hertsig, van den Wildenberg, & Hommel, 2010).

4.3.3. Study procedure

Prior to study participation, a T1-weighted anatomical scan was acquired for all TMS-eligible participants[73]. Each participant completed five separate sessions that are summarised in Figure 4.4. TMS across all sessions were delivered via a 70mm Figure-8 coil and a Magstim Rapid^2 biphasic stimulator (The Magstim Company Ltd, UK). Specific session information is outlined below.

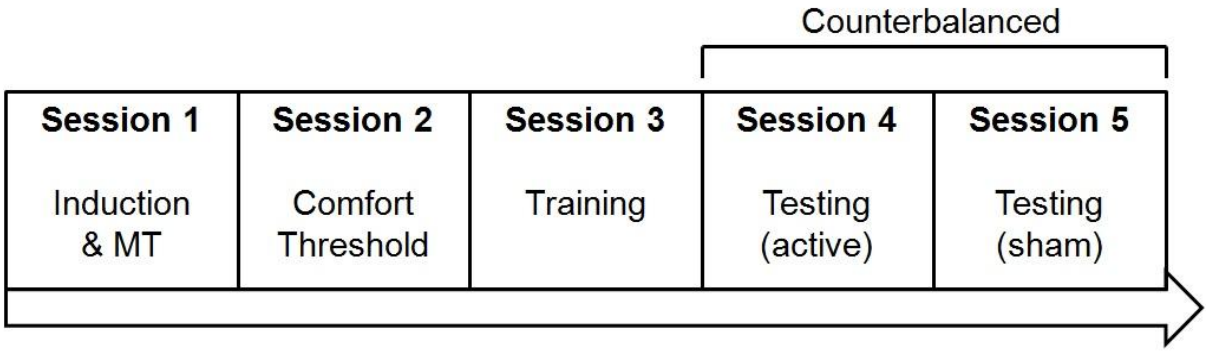


Figure 4.4. The order of sessions completed by each participant. **MT**= motor threshold, **active**=active cTBS applied to the rIFG, **sham**= control cTBS application (baseline). The order of active and sham testing sessions were counterbalanced across participants. Total participation time across all sessions was 13.5 hours.

4.3.3.1. Session 1: Induction and motor threshold

During an initial induction session, participants were screened to ensure adherence to all TMS and MRI safety guidelines (Maizey *et al.*, 2013, APP2.1)[74]. Right-hemisphere motor thresholds (MT) were acquired during this session, using the observation of movement method (Stokes, Chambers, Gould *et al.*, 2005, 2007; Varnava, Stokes, & Chambers, 2011). Here, the TMS coil was placed tangentially on the scalp surface over the motor region and oriented 45˚ away from the midline. The position of the TMS coil was varied until the application of TMS pulses induced reliable twitches in the contralateral hand. The applied TMS intensity was varied using an adaptive staircase

[73] T1-weighted scans are acquired before all TMS studies in accord with in-house procedures. If not previously acquired the protocol for acquisition was in accord with that outlined in Section 4.3.3.4.1 (pre-cTBS protocol).

[74] Note that, inductions, motor thresholds and comfort thresholds are conducted prior to all TMS studies conducted at Cardiff University Brain Research Imaging Centre (CUBRIC). As such, if individuals have previously participated in TMS studies at CUBRIC they may have been exempt from these components of the current study if the relevant safety and threshold procedures had already been completed.

method until 5 of 10 successive pulses delivered over the motor cortex elicited a twitch. MT was defined as the corresponding stimulator intensity.

The distance between the scalp and the cortex can influence the strength of the TMS-induced electromagnetic field at the site of application (Stokes *et al.*, 2005, 2007; Stokes, Barker, Dervinis *et al.*, 2013). To account for individual variations in scalp-cortex distance between M1 and rIFG, TMS output intensities were adjusted using a correction of 2.7% per mm as recommended by Stokes *et al.* (2013). This approach takes advantage of the linear relationship between the TMS-induced electric field and scalp-cortex distance (Stokes *et al., 2*005, 2007, 2013) and enhances the sensitivity of TMS by taking into account individual variation in susceptibility to TMS effects (Stokes *et al., 2*013). Additionally, the use of % adjustments of MT normalises the intensity across subjects making the effects comparable (Robertson, Théoret, & Pascual-Leone, 2003).

Distances between the cortex and scalp coordinates for M1 and rIFG were calculated, separately, as the Euclidean distance:

$$\text{Euclidean Distance} = \sqrt{((X_2 - X_1)^2 + (Y_2 - Y_1)^2 + (Z_2 - Z_1)^2)}$$

where X, Y and Z coordinates for the scalp (2) and cortex (1) were used. Distance adjusted MT (AdjMT) for the rIFG was computed as:

$$AdjMT\% = 2.7 \times (D_{rIFG} - D_{M1}) + MT_{M1}$$

where AdjMT is the adjusted MT in % of stimulator output, MT is the unadjusted MT in % stimulator output, D_{M1} is the distance between the scalp location and M1, D_{rIFG} is the distance between the scalp and the cortical location of the rIFG, and 2.7 refers to the % correction factor (Stokes *et al., 2*005, 2013).

4.3.3.2. Session 2: Comfort threshold

When applied to frontal sites TMS is often associated with pain and discomfort due to the dense muscularity at the front of the head and possible aggravation of the trigeminal nerve (Machii, Cohen, Ramos-Estebanez, & Pascual-Leone, 2006; Ropohl, Hiller, Sperling *et al.*, 2004; Wassermann, 1998). A comfort threshold procedure was employed to confirm that the administration of cTBS to the rIFG at the target level was

comfortable for participants. As per Verbruggen *et al.* (2010), the target intensity for cTBS application was 80% AdjMT, but a lower benchmark of 60% AdjMT threshold was accepted if discomfort was experienced.

Prior to the comfort threshold the rIFG was localised for each individual using their specific T1-weighted anatomical scan as outlined by Verbruggen *et al.*,(2010; see Figure 4.5). A miniBird 500 and MRIcro/MRIreg software were used to co-register the rIFG position with its corresponding scalp location for each participant (Ascension Tech, US).

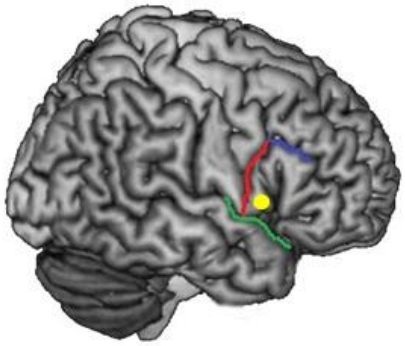


Figure 4.5. Landmarks used to anatomically localise the rIFG as per the method outlined by Verbruggen *et al.* (2010). The rIFG was located separately for each participant and defined as the region directly anterior to the precentral sulcus (red) and ~20% of the total distance between the inferior frontal sulcus (blue) and lateral sulcus (green). The site of cTBS application corresponds to the yellow dot.

The comfort threshold procedure involved the application of single TMS pulses and short bursts of TMS applied via a staircase method to the rIFG. As per Verbruggen *et al.* (2010), the coil was positioned tangentially on the scalp with the coil handle oriented upward (see Figure 4.7a). Initially, the stimulator output was set to administer single pulses at 30% output (or lower if target intensity was below this). 5 single pulses of TMS were applied to the rIFG: 1 every 3 seconds. If no discomfort was reported then the stimulator was set to administer 5 bursts of 3 pulses at 50Hz with 200ms intervals (equivalent to 15 pulses)[75]. If no discomfort was reported, the stimulator output was increased by 2% (or lower if target intensity was below this), and the procedure repeated. If discomfort was reported at any stage, the stimulator output was decreased by 1% until the applied intensity was reported comfortable by the participant. The stimulator intensity to be used in the testing sessions either corresponded to the target

[75] This protocol is a reduced version of that used for cTBS. The aim is to provide participants an experience similar to that associated with cTBS application.

intensity (if achieved) or to the maximum stimulator output where no discomfort was reported. Participants were excluded if discomfort was reported at TMS intensity below 60% AdjMT.

4.3.3.3. Session 3: Training

As per Study 1, participants completed a training session prior to testing. The training procedure is outlined in Section 2.2.3, but the IT was omitted from the current study. This was to ensure as many SST and DT trials were included within the time-frame in which cTBS exerts its effects as possible (1 hour; Huang *et al., 2*010). Furthermore, activity associated with the IT in Study 1 was found to also be common to both inhibitory and non-inhibitory action updating requirements. Six blocks of the SST and six blocks of the DT were presented in an interleaved order during each behavioural run for mixed training and testing. Order of tasks was counterbalanced across subjects, but maintained within subjects. As per Study 1, inhibition functions for testing were set according to training data for each participant individually (Section 2.2.3).

4.3.3.4. Sessions 4 and 5: Testing

Testing sessions took place in a 3T GE HDx scanner, equipped with an 8-channel head coil. The order of events within each session is outlined in Figure 4.6. Due to the time-varying effects of cTBS (see Section 4.2.3.1), post-cTBS MRS and fMRI runs were acquired at consistent times both within and across participants. I aimed to begin the first, second, third and fourth post-cTBS acquisitions at 15, 29, 43 and 57 minutes post-cTBS application, respectively (see Figure 4.6).

Participant position, presentation of stimuli and acquisition of physiological measures were as in Study 1 (Section 2.2.3), but the adjustment of SSDs/SOAs occurred after every run as opposed to every second. Responses were made using a NATA response box (NATA Technologies, Canada). Crucially, to prevent modulation of behavioural performance other than provided by the intervention (i.e. cTBS) no feedback was provided during the testing sessions. Consequently, participants could not be excluded due to behavioural performance decrements within the either the active or

sham testing sessions. Exclusion criteria at the group level for baseline performance (i.e. that during the sham session) still applied (APP10.3.2).

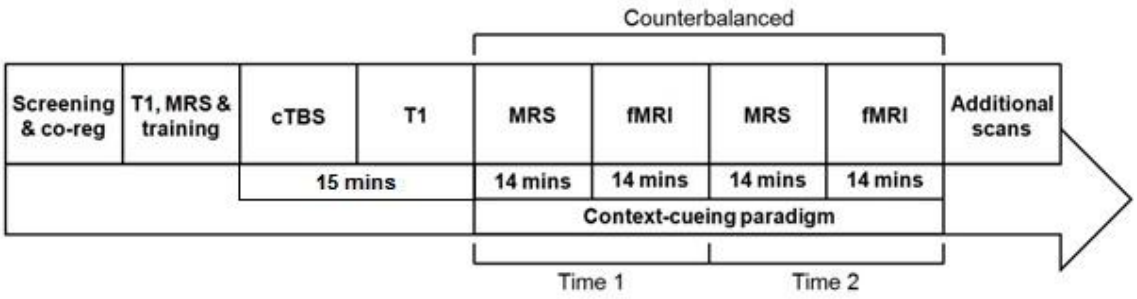


Figure 4.6. Order of events within each testing session. Participants were initially screened for TMS and MRI contraindications and individual rIFG coordinates co-registered to the corresponding scalp location (for both active and sham sessions). An initial T1-weighted structural scan was acquired followed by the acquisition of a pre-test Magnetic Resonance Spectroscopy (MRS) acquisition. During this time participants completed a training block of each of the tasks. cTBS was applied in either the active or sham orientation (Section 4.3.3.3.4.2) in the control room. The post-cTBS scans commenced with the acquisition of a second T1-weighted anatomical scan. Subsequent MRS and functional Magnetic Resonance Imaging (fMRI) acquisitions were interleaved. Whether MRS or fMRI was acquired first was approximately counterbalanced across participants (but order maintained within subjects). The time allocated for the preparation and acquisition of each MRS/fMRI scan is also shown. Time 1 and time 2 relates to the separation of time for exploratory analyses (Section 4.5.4.1). Additional scans were acquired at the end of each session (see Section 4.3.3.5).

4.3.3.4.1. Anatomical scans

T1-weighted 3D FSPGRs were acquired pre- and post-cTBS for each testing session. This helped facilitate MRS voxel placement, ensuring precise localisation both within and between sessions (Section 4.3.3.4.4.1). Anatomical scans were acquired in a true axial orientation and the protocols used were:

- **Pre-cTBS:** Field of View (FOV): 256mm, 256x192x172 (1mm isotropic), repetition time (TR)=7.8ms, echo time (TE)=3ms, inversion time (TI)=450ms. No parallel imaging.

- **Post-cTBS:** FOV: 256mm, 256x192x172 (1mm isotropic), TR=7.8ms, TE=3ms, TI=450ms. Parallel imaging acceleration factor 2.

The difference between the pre- and post-cTBS anatomical scans lies in the speed in which they are acquired. As the post-cTBS phase of the testing sessions was time

critical, the post-cTBS anatomical scan was acquired at a faster rate than the pre-cTBS anatomical scan (3 minutes 40s, compared with 7 minutes 20s). The increase in speed leads to a reduction in the signal-to-noise ratio of the final image (lower in the post-cTBS FSPGR by 2^0.5).

4.3.3.4.2. cTBS protocol

cTBS was administered at 80% AdjMT (or lower if discomfort reported, Section 4.3.3.2) in bursts of 3 pulses applied at 50Hz at 200ms intervals (i.e. 5Hz) until a total of 600 pulses were administered within 40 seconds (Huang *et al.*, 2005). Coil orientation was dependent on whether active or sham cTBS was applied (Figure 4.7).

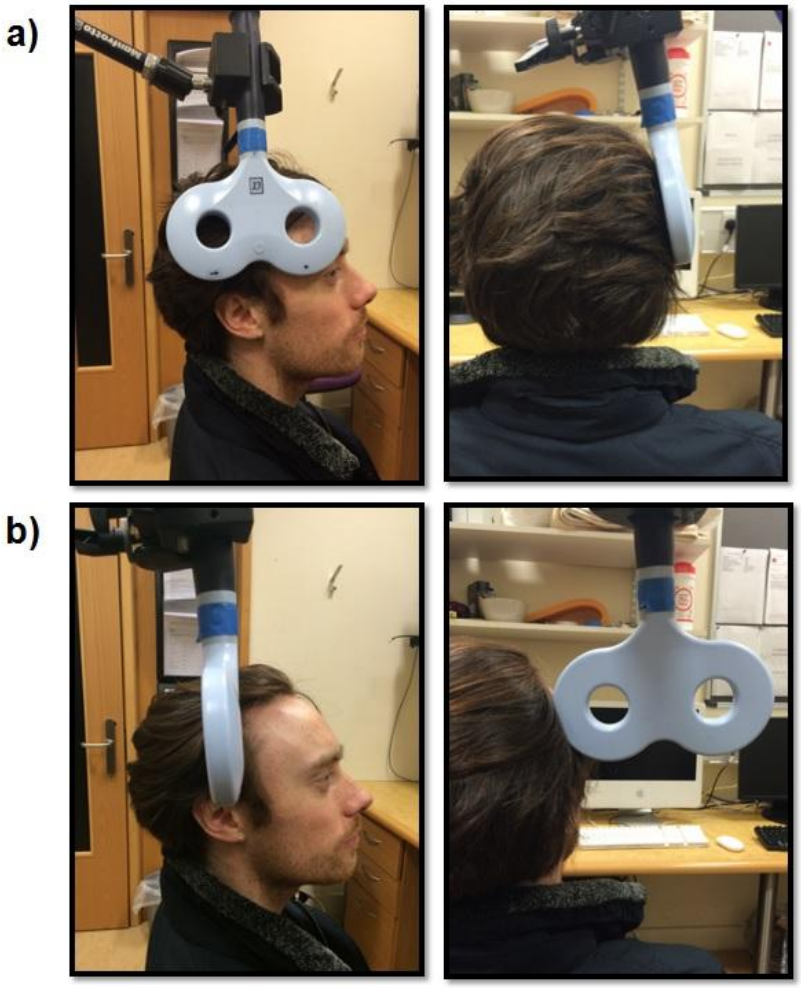


Figure 4.7. The orientation of the TMS coil during active **(a)** and sham **(b)** testing conditions. During active stimulation the coil was positioned tangentially to the scalp with the handle facing upwards (as per Verbruggen *et al., 2*010). During sham stimulation the coil was oriented 90°away from the scalp surface so that only one wing of the coil was in contact with the scalp surface. This orientation has been shown to minimise the magnetic flux reaching the cortex (Lisanby *et al*, 2002).

4.3.3.4.3. fMRI protocol

Whole-brain functional images were acquired using an echo planar imaging (EPI) sequence with AC-PC alignment (TR=3000ms, TE= 35ms, matrix size 64 × 64, flip angle 90° in-plane resolution 3.4mm × 3.4mm, 3.4mm slice, no gap, parallel imaging factor = 2). Interleaved slices were acquired in an ascending direction. 204 volumes[76] were acquired over the course of each run (2 fMRI runs were acquired in each testing session, such that a single fMRI run covered the duration of a single behavioural run). Each run was preceded by the acquisition of 4 dummy scans, to allow for T1-equilibrium (the first task cue was presented during this time).

4.3.3.4.4. MRS protocol

GABA-edited MEGA-PRESS spectra (Mescher, Merkle, Kirsch *et al.*, 1998) were acquired with the following parameters: voxel size=30x30x30mm; TE= 68ms; TR= 1800ms; acquisition bandwidth= 5kHz, 4096 Free Induction Decay points, 16ms editing pulses alternating at 1.9 ('on') and 7.5ppm ('off' pulse symmetric about the water peak) to separate the GABA molecule from other chemicals (Puts and Edden, 2012), 2 step phase cycling, 332 averages and 8 water reference scans. Acquisition time was 10 minutes 34 seconds. Justification for the use of MRS and GABA-edited protocols are outlined in APP10.3.3.

4.3.3.4.4.1. MRS voxel placement.

Voxel location was prescribed based on the corresponding pre- or post-cTBS FSPGR of each session. Initially, the pre-cTBS reformatted FSPGR was used to position the MRS voxel. To acquire as much signal from the entire rIFG region (including both the *pars opercularis* and the *pars triangularis*), I endeavoured to centre the MRS voxel over the right anterior ascending ramus, with the inferior surface of the voxel positioned over the intersection of the right anterior ramus and the lateral sulcus with a true axial

[76] Technical issues meant that for a single participant, one of their fMRI runs consisted of 202, rather than 204, volumes.

orientation. This voxel placement ensured coverage of the rIFG as per Verbruggen *et al.*'s definition (see Figures 4.5 and 4.8) and site of cTBS application. The voxel was positioned away from the scalp surface to prevent contamination of spectra from non-brain tissue. Screen shots were used to facilitate consistency in voxel placement between pre- and post-cTBS MRS acquisitions and across testing sessions.

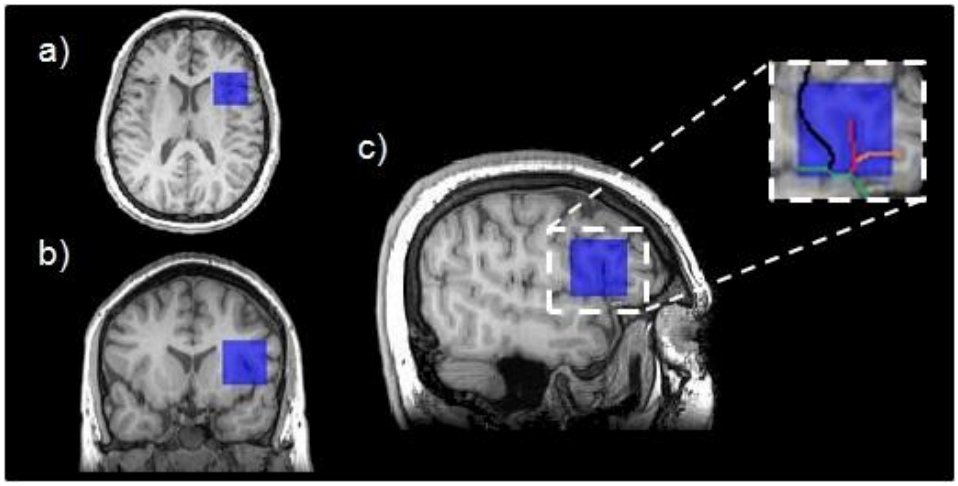


Figure 4.8. An example of the placement of the MRS voxel in the **(a)** axial plane, **(b)** coronal plane and **(c)** sagital plane. The callout box in **(c)** illustrates the anatomical landmarks used to position the MRS voxel in the right hemisphere. Black line= precentral sulcus, red line= anterior ascending ramus, orange line= anterior horizontal ramus, green line=lateral suclus. The voxel was placed in a true axial orientation and positioned away from the scalp surface to prevent contamination from non-brain tissue.

4.3.3.5. Post-test acquisitions

At the end of each testing session a field map was acquired to reduce any spatial distortion of the EPI images post-hoc (3D spoiled, gradient-recalled echo sequence, TR=20ms, TE=7ms and 9ms)[77].

4.4. Statistical analyses

The computation of behavioural dependent variables was as per Study 1 (Section 2.3.1). Here, SSRTs were estimated using the integration method (Logan & Cowan, 1984)

[77] Due to technical difficulties, fieldmap acquisition was compromised for 8 participants. For these participants fMRI analyses were conducted without fieldmaps for both testing sessions. This was to prevent bias during processing in any one condition. Compromised fieldmaps were not acquired at a later date because the information required for un-warping is dependent on participant head geometry and orientation within the scanner at the time of the scan.

only[78]. All DVs were calculated separately for each behavioural run as well as averaged across MRS/fMRI runs within a testing session for further analysis. Difference tests were computed to establish whether dependent measures varied between the sham vs. active testing sessions. Correlations were used to establish the presence of relationship between measures at baseline or those modulated by cTBS. For the latter analyses, Δ was computed via the subtraction of sham from active scores for each of the dependent variables. Data screening was conducted as per Study 1 (Section 2.3.3).

4.4.1. fMRI Analyses

As per Study 1, both whole brain and region of interest (ROI) analyses were used to test whether BOLD activity was modulated by cTBS and, if so, how. Pre-processing of data was as outlined in Section 2.3.2.1, with the exception that no spatial smoothing was applied. This was to prevent the spatial distortion of BOLD signals between regions in close proximity (e.g. STN and SN; de Hollander *et al.*, 2015). All events were modelled from the onset of each arrow or fixation stimulus as applicable.

Planned contrasts were undertaken to test the replicability of the pattern of activity associated with inhibitory and non-inhibitory action updating found in Study 1 and to assess whether cTBS was able to modulate general activity across the whole brain (Table 4.1; additional contrasts were computed to replicate the pathways analyses outlined in Chapter 3; see Chapter 5). No-signal trials within each context and fixation crosses that appeared across both contexts provided baselines. Multiple baseline options were selected as the contrasts from which to extract the BOLD signal change may influence what can be inferred regarding the underlying neural activity (Mostofsky & Simmonds, 2008). The signal to noise ratio may also differ with between baseline options (Welvaert & Rosseel, 2013). Contrasts were conducted separately for active and sham sessions. Resulting BOLD activity at the whole brain level was compared between active and sham sessions with paired sample t-tests in FEAT. Note that those contrasts involving all fixations were not entered into t-tests as the multiple baseline options were

[78] The mean method was omitted here as previous work has shown the mean method to potentially overestimate SSRT (Verbruggen *et al.*, 2013) and was found to provide larger SSRTs relative to the integration method in Study 1. Additionally, the integration method was used in the study by Verbruggen *et al.* (2010).

for use with ROI analyses aimed at exploring potential GABA/BOLD correlations only[79].

4.4.1.1. Region of interest analysis

ROIs were identified as per Study 1 (Sections 2.3.2.2 and 3.2.1) and analyses aimed to establish if the magnitude of BOLD activity (measured as %BOLD) within the rIFG was modulated by cTBS and whether this was related to behavioural measures of inhibitory and non-inhibitory action updating (SSRT and DRT2, respectively) and GABA concentration. Predominantly, I was interested in BOLD activity local to the site of cTBS application, the rIFG. Featquery in FSL was used to extract the mean %BOLD associated with the signal>no-signal contrasts in the SST and DT for both active and sham sessions (and each separate fMRI run)[80]. Exploratory analyses aimed to establish if the pattern of activity resembling the putative pathways identified in Chapter 3 could be replicated and whether cTBS was able to modulate %BOLD in remote ROIs (preSMA, STR, GPe, GPi, SN, STN and THAL).

[79] For these analyses I was interested in %BOLD associated with action updating, but it was not essential that the baseline control for other processes as the primary concern was whether GABA/BOLD relationships were evident.

[80]Note that %BOLD in the vicinity of the rIFG was also extracted for the stop signal> all fixations and double signal>all fixations contrasts for the BOLD/GABA correlation analyses (see Table 4.1).

Table 4.1. Planned contrasts, conjunction and disjunction analyses of fMRI data.

Analysis	Purpose
SS>SNS	To identify regions of activation associated with inhibitory action updating. To be used in analyses for the replication of Study 1 and region of interest analyses outlined in Sections 4.5.2 and 4.5.4.2.
DS>DNS	To identify regions of activation associated with non-inhibitory action updating. To be used in analyses for the replication of Study 1 and region of interest analyses outlined in Sections 4.5.2 and 4.5.4.2.
SS>FA	To identify regions of activations associated with inhibitory action updating. The use of FA here was to obtain an additional baseline measure from which to extract the %BOLD for the GABA/BOLD correlations in Section 4.5.2.
DS>FA	To identify regions of activations associated with non-inhibitory action-updating. The use of FA here was to obtain an additional baseline measure from which to extract the %BOLD for the GABA/BOLD correlations in Section 4.5.2.
(SS>SNS) ∩ (DS>DNS)	To identify regions of activation common to both inhibitory and non-inhibitory action updating. To be used in analyses pertaining to the replication of Study 1 (Chapter 5).
(SS>SNS) NOT (DS>DNS)	To identify regions of activation specific to inhibitory action updating in the absence of non-inhibitory action updating. To be used in the analyses for the replication of Study 1 (Chapter 5).
(DS>DNS)NOT (SS>SNS)	To identify regions of activation specific to inhibitory action updating in the absence of inhibitory action updating. To be used in the analyses for to the replication of Study 1 (Chapter 5).

Note. **SS**= stop signal, **SNS**=stop no-signal, **DS**= double signal, **DNS**= double no-signal, **FA**= all fixations, ∩= conjunction, **>**= conventional contrasts where BOLD activation patterns are greater under one condition relative to another, **NOT** = disjunction (refers to the logical not rather than a subtraction. These analyses differ from conventional contrast approaches due to the removal of active supratheshold voxels yielded in one contrast from another. In effect, disjunction analyses remove regions of overlapping activity between contrasts of interest). Although disjunction and conjunction analyses were not pre-registered as part of the current study, these were computed as a means to provide a more in-depth replication of Study 1 than would have otherwise been possible (see Section 5.1.1.).

4.4.2. GABA quantification

GABA concentration is typically quantified in relation to an internal reference[81] (Jansen, Backes, Klaas, & Kooi, 2006). Creatine (Cr) was used as the reference metabolite in the current study (see APP10.3.4 for justification). The GABA-edited MRS data were analysed via the Gannet toolkit (version 2.0; Edden, Puts, Harris *et al*, 2014). Gannet uses the GABA-edited difference spectrum to estimate GABA concentration and the unedited 'off' spectrum to estimate Cr concentration[82] in institutional units relative to water. A Gaussian peak with a linear baseline is fitted to the GABA-edited peak and a Lorentzian peak and linear baseline fitted to the Cr peak at 3ppm. The area between the Gaussian and linear fits provide estimates of the relevant metabolite concentrations (Edden *et al., 2*014). As I was aware of the cTBS conditions under which the GABA spectra were acquired, a blinded analyst – Dr C. J. Evans (MRI lab manager at CUBRIC) – inspected the data for artefacts and rejected spectra that would likely affect GABA quantification. If data quality was deemed insufficient and rejected for either pre-cTBS spectra within a session and/or both post-cTBS spectra within a session, then the session was re-run[83].

For each session GABA concentration was calculated separately for each MRS acquisition. The pre-cTBS acquisition provided a baseline concentration for those acquired post-cTBS as a means to remove day-to-day variation in GABA concentration (as per previous work, e.g. Allen *et al.*, 2014) [84].

GABA concentration = (post-cTBS GABA – pre-cTBS GABA)

To isolate cTBS-induced effects, the GABA concentration was double-baselined using both the within session pre-cTBS MRS acquisition and that acquired during the sham session:

Δ GABA concentration = (active post-cTBS GABA – active pre-cTBS GABA) – (sham post-cTBS GABA – sham pre-cTBS GABA)

[81] Differences between hardware (e.g. coils and gradients), field strength and participant-related variables (e.g. head position) can influence the quantification of metabolites yielded by MRS. It is presumed that these factors will affect all metabolites in the same way. Thus, the use of an internal reference can establish consistency in inferences between participants, scanners and studies (de Graff, 2007).
[82] Water is also available as a reference concentration but was not used in the current study.
[83] Three sessions were repeated overall.
[84] Note that due to time restrictions it was not feasible to obtain stable pre-cTBS estimates of either our behavioural measures or %BOLD.

Baseline GABA was analysed using the data acquired from the sham session only. Existing literature shows a wide range in the dependence of the GABA measurement on voxel tissue grey matter/white matter (GM/WM) composition, with pure GM GABA concentration estimated to be between 2-10 times higher than in white matter (Bhattacharyya, Phillips, Stone, & Lowe, 2011; Choi, Bhardwaj, Kalra *et al.*, 2007). The reference metabolite (Cr), is also shown to be higher in GM than WM (Maudsley, Domenig, Govind *et al.*, 2009), albeit with a weaker dependence on tissue GM/WM content (approximately 10%). This uncertainty makes it inappropriate to 'correct' the GABA/Cr values based on voxel GM/WM composition. As this is a within-participant design, with the MRS voxel prescribed to be consistent between the active and sham testing conditions, I anticipated no systematic bias introduced by GM differences. As such the values are reported without correction or co-varying for GM fraction. The % overlap of the MRS voxels within sessions was calculated to ascertain consistency in voxel placement within participants.

4.5. Results

Results reported here refer to parametric analyses and Bayesian equivalents. Non-parametric tests (if required) and analyses subsequent to outlier removal are reported in APP10.3.6. Any discrepancies between findings are discussed. Note that for any BFs calculated for GABA-related data the prior scale factor was reduced by $\sqrt{2}$[85].

I initially report the results of the behavioural data acquired from the sham sessions only to demonstrate that participants conformed to task instructions and performance was in accord with that observed in Study 1 (Section 2.4.1). I then report results of the difference tests to assess whether dependent measures varied between active and sham cTBS sessions. The relationships between measures (at baseline and cTBS-induced) are then detailed. Finally, exploratory analyses are reported. These analyses include exploration of cTBS-induced changes in dependent measures over time, the effect of cTBS on %BOLD in ROIs remote to the site of cTBS application and analyses aimed at replicating the main findings from Study 1.

[85]Based on personal communication with R. Morey (Cardiff University). Justification of use of $\sqrt{2}$ comes from noting that (assuming equality and independence of the errors) $sd(X - Y) = \sqrt{(var(X - Y))} = \sqrt{(var(X) - var(Y))} = \sqrt{(2 * var(X))} = \sqrt{(2)} * sd(X)$, if sd(X) is the error. Since the error will be increased by $\sqrt{(2)}$, the effect size will be decreased by $\sqrt{(2)}$.

4.5.1. Baseline results

At baseline (sham cTBS condition) behavioural analyses revealed results consistent with Study 1 (Section 2.4.1). As per previous work (e.g. Verbruggen *et al., 2*010), mean RTs to signal trials in the SST (where participants incorrectly executed a response), were faster than to no-signal trials ($t_{(29)}$=6.27, $p_{.025}$<.001, BF=22852). Mean RTs of the first response on double-signal trials were slower than to double no-signal trials ($t_{(29)}$=7.13, $p_{.0167}$<.001, BF=194409). Stop no-signal RTs were found to be longer than double no-signal RTs ($t_{(29)}$=3.07, $p_{.05}$=.005, BF=8.64). Accuracy was within pre-specified benchmarks of >85% for all no-signal trials (stop no-signal: *M*= 97.86%, *SD*= 1.48%; double no-signal: *M*=97.25%, *SD*=1.73%) and double-signal trials (*M*=94.24%, SD=4.19%). Successful inhibition occurred on ~50% of stop signal trials (*M*=44.78%, *SD*=7.3%) validating the efficacy of the inhibition functions used to set SSDs (adjusted R^2= 0.96, *SD*=0.04). SSRT estimates using the integration method was 251.34ms (*SD*=36.3ms) in agreement with previous studies with similar mean no-signal RTs (here *M*=452.86ms, *SD*=46.55ms, e.g. Study 1 and Verbruggen *et al., 2*010). In the DT, reliable PRPs were found for all participants (adjusted R^2= 0.71, *SD*=0.24). The mean DRT2 at the shortest, intercept and longest SOAs significantly different from one another ($F_{(1.26,36.56)}$=176.4, *p*<.001, Greenhouse-Geisser corrected, BF=1.25^{e+24}), where DRT2 at the shortest SOA was greater than DRT2 at the intercept ($p_{.017}$<.001, BF=1.06^{e+15}) and than that at the longest SOA ($p_{.025}$<.001, BF=8.74^{e+9}). There was no significant difference between DRT2 at the intercept and the longest SOA (*p*=.312, BF=0.32).

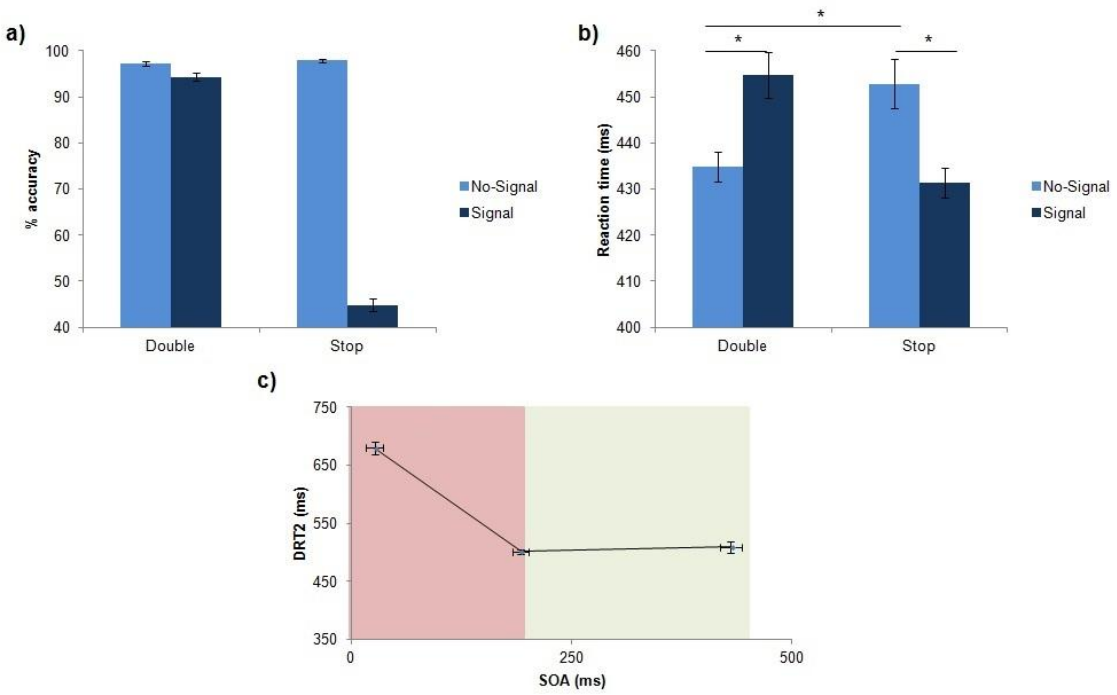


Figure 4.9. (a) Accuracy and **(b)** mean reaction times across all trial types. In **(b)** the signal RTs in the double task refer to the first response on double-signal trials and the signal RTs in the stop task refer to failed stops. The mean psychological refractory period effect found across participants is represented in panel **(c)**. The time to execute the second response relative to the signal onset (DRT2) was found to decrease as the delay between stimulus and signal onsets (SOA) increased during the pre-bottleneck stage (pink area), relative to the post-bottleneck stage (green area). Pre- and post-bottleneck stages were identified based on the intercept between weighted linear fits and the mean RT on no-signal trials in the DT. *****=significant difference according to Holm-Bonferroni adjusted α. Error bars= ±1 within subject standard error (Cousineau, 2005; with correction, Morey, 2008).

4.5.2. The effects of cTBS applied to the rIFG

cTBS was applied between 60% and 74.29% AdjMT (*M*=65.23%, *SD*=4.58%; equivalent to 30-47% of absolute stimulator output; mean MNI co-ordinates= 60, 13, 6). Subject-specific details can be found in Table APP10.3.1. fMRI and MRS acquisitions commenced at 15 minutes 7 seconds, 29 minutes 7 seconds, 43 minutes 3 seconds and 57 minutes and 2 seconds for runs 1, 2, 3 and 4 post-cTBS, respectively. There was no difference between the onset times for each run between active and sham sessions (all $p>.1$, all BFs<0.69).

Contrary to expectations, the application of cTBS to the rIFG was not found to modulate any of the dependent measures (Table 4.2 and 4.3). Corresponding BFs suggest evidence largely in favour of the null. However, BFs indicate the evidence to be

inconclusive for an effect of cTBS on GABA (BF=0.5[86]; 60% of all participants showed elevated rIFG GABA after active cTBS relative to sham cTBS). It is possible that this result is a combination of inter-individual differences in susceptibility to cTBS (e.g. Hamada, Murase, Hasan *et al.,* 2013) combined with difficulty in quantifying GABA reliably in the frontal cortex (de Graff, 2007). The latter point is highlighted by the poor within and between session repeatability and high variability in GABA concentration both within and between participants (Table 4.4). This is unlikely to be due to poor MRS voxel placement between pre- and post-cTBS acquisitions as the mean fractional overlap of pre- and post- voxels was 77.93% (*SD*=9.15%) within sessions[87].

Table 4.2. Mean and standard deviations for all dependent variables acquired in the sham and active testing sessions.

	Sham		Active	
DV	Mean	SD	Mean	SD
% SNS	97.86	1.48	97.66	2.18
% DNS	97.25	1.73	97.18	2.22
% SS	44.78	7.3	43.4	6.87
% DS	94.24	4.19	93.75	5.68
SNS RT	452.86	46.55	451.73	50.41
DNS RT	434.82	31.47	434.79	37.76
SSRT	251.34	36.3	256.84	47.13
DRT1	454.07	33.49	454.46	40.4
DRT2	552.25	49.55	551.67	60.82
GABA	-0.005	0.02	0.001	0.02
%BOLD (Stop)	0.2	0.23	0.19	0.17
%BOLD (Double)	0.11	0.22	0.08	0.16

Note. **DV**= dependent variable; **SD**=standard deviation; **%**= percent correct; **SNS**= stop no-signal trials; **DNS**= double no-signal trials; **SS**= stop signal trials; **DS**= double signal trials; **RT**= reaction time in ms; **SSRT**= stop-signal RT; **DRT1=** RT of the initial response on double signal trials; **DRT2**= onset of the additional response on double signal trials minus the signal onset asynchrony; **GABA**=GABA concentration in institutional units; **%BOLD**= blood oxygen level dependent signal change in the rIFG. %BOLD was extracted from signal>no-signal contrasts in either the SST or DT.

[86] BF increases to 1.36 after outlier removal. See APP10.3.6.1.

[87] No difference in the % overlap between pre- and post-cTBS MRS voxels was found between the active and sham cTBS sessions ($t_{(29)}$=-1.38, *p*=.178, BF=0.46). Note overlap was greater in the sham relative to active cTBS conditions after outlier exclusion and with non-parametric tests. See APP10.3.6.1.

Table 4.3. Paired sample t-tests for each dependent measure acquired in the active vs. sham testing sessions.

DV	t	*p*	BF
% SNS	-0.64	.529	0.23
% DNS	-0.31	.763	0.2
% SS	-1.48	.150	0.52
% DS	-0.64	.528	0.24
SNS RT	-0.2	.841	0.2
DNS RT	-0.01	.994	0.19
SSRT	1.04	.305	0.32
DRT1	-0.05	.965	0.2
DRT2^{+}	-0.27	.787	0.2
GABA^{+}	1.23	.228	0.5
%BOLD (Stop)	-0.34	.734	0.21
%BOLD (Double)	-0.73	.469	0.25

Note. **DV**= dependent variable; **t**=t-value; ***p***=p-value; **BF**=Bayes Factor; **%**= percent correct; **SNS**= stop no-signal trials; **DNS**= double no-signal trials; **SS**= stop signal trials; **DS**= double signal trials; **RT**= reaction time; **SSRT**= stop signal reaction time; **DRT1=**reaction time of the initial response on double signal trials; **DRT2**= reaction time of the additional response on double signal trials minus the signal onset asynchrony; **%BOLD**= blood oxygen level dependent signal change in the rIFG. BOLD was extracted from signal>no-signal contrasts in either the SST or DT. Note that for any BFs calculated for GABA-related data the prior scale factor was reduced by √2 (see section 4.4.2). **$^{+}$=** analysis conducted on transformed data. α-level not shown as all *p*>.05.

Table 4.4. Indices of the reliability and variability analyses of GABA quantification acquired within and between sessions.

	ICC	CVwp	CVbp
Within sessions	-0.2	11.43	11.57
Between sessions	0.25	11.73	13.92

Note. The procedure for reliability and variability computations can be found in APP10.3.6.4. **ICC**= intraclass correlation coefficient (analysed using a 2-way random model for absolute agreement); **CVwp**= coefficient of variation within participants; **CVbp**= coefficient of variation between participants. Here, within session refers to the post-cTBS MRS acquisitions in the sham session and between sessions refers to the pre-cTBS MRS acquisitions acquired in the sham and active sessions.

Repeated measures ANOVA revealed no influence of cTBS (active vs. sham) on DRT2, when divided according to within- and post-bottleneck phase. No main effect of

cTBS on DRT2 ($F_{(1,28)}$=0.8, p=.379, BF=0.23) and no interaction effect between cTBS and bottleneck phase ($F_{(1,28)}$=0.01, p=.916, BF=0.27) was demonstrated. A significant main effect of within- vs. post-bottleneck phase was identified, although expected given the presence of the PRP at short relative to long SOAs ($F_{(1,28)}$=283.07, p<.001, BF=1^{e+21}; see also Figure 4.9c). The size of the bottleneck was also found not to differ between active and sham sessions ($t_{(29)}$=1.25, p=.221, BF=0.39) and although the location of the intercept appeared later in active vs. sham cTBS sessions (indicated by longer SOA: *M*=216.27ms, *SD*=51.89ms vs. *M*=192.31ms, *SD*=54.53ms) this was not reliable ($t_{(29)}$=1.82, p=.079, BF=0.83).

Bayesian meta-t-tests (Rouder & Morey, 2011) were conducted to fully ascertain whether cTBS was found to modulate any of the behavioural measures across the current study and that by Verbruggen *et al.* (2010). Resulting BFs (Table 4.5) indicate evidence in favour of an effect of cTBS on SSRT, although more data is required to substantiate this. Evidence also indicates that cTBS has no effect on simple RTs as BFs were in favour of the null (i.e. <1/3).

Table 4.5. Bayes Factors corresponding to Bayesian meta t-tests conducted on behavioural dependent variables.

DV	BF
SSRT	2.39
DRT2	0.28
DRT1	0.29
SNS RT	0.36
DNS RT	0.29

Note. Bayesian t-statistics computed for the dependent variables (DVs) in the current study and those provided by Verbruggen *et al.* (2010) were analysed. **BF**=Bayes Factor; **SSRT**=stop signal reaction time, **DRT2**=the latency of the additional response on double-signal trials; **DRT1**= the latency of the initial response on double-signal trials; **SNS RT**= reaction time to no-signal trials in the SST; **DNS RT**= reaction time to no-signal trials in the DT. The values from Verbruggen *et al.* (2010) entered into the analyses for no-signal RTs corresponded to go RTs collapsed across SST, DT and IT. The prior scale factor used here was r=1 as recommended by Rouder & Morey (2011).

Paired sample t-tests revealed no significant effects of cTBS on BOLD activity at the whole-brain level (Figure 4.10). The pattern of activity corresponding to inhibitory and non-inhibitory action-updating was well matched across the active and

sham sessions and no clusters signifying a difference in activations between these conditions were found.

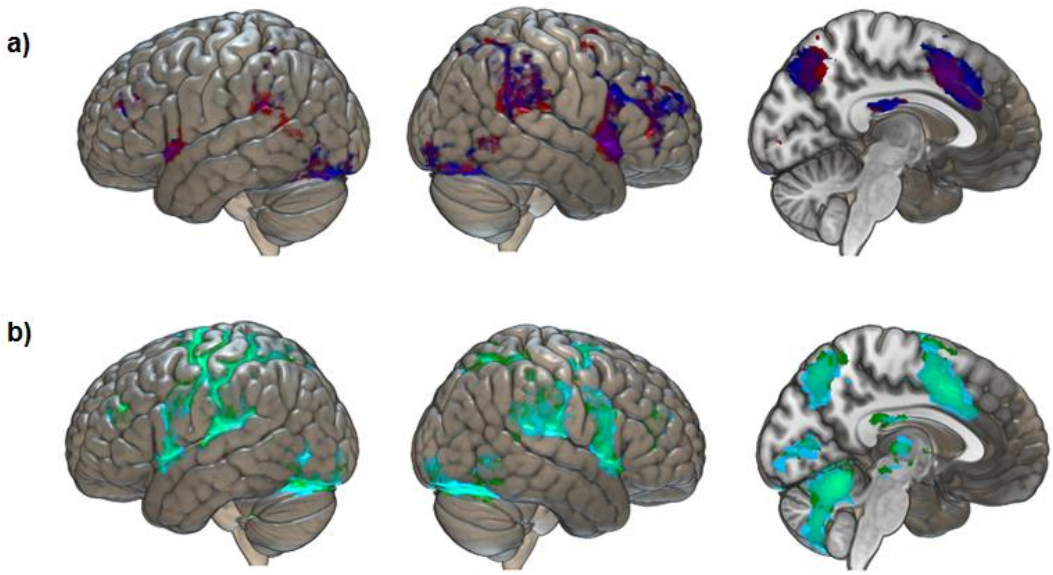


Figure 4.10. The overlap in activity produced under active and sham cTBS conditions using the contrasts stop-signal > stop no-signal **(a)** and double-signal > double no-signal **(b)**. Activity under sham cTBS conditions are outlined in red **(a)** and green **(b)**. Activity under active cTBS conditions are outlined in blue for both **(a)** and **(b)**.

4.5.3. The relationship between dependent variables

To establish whether there were any relationships between dependent measures a series of correlation analyses were conducted using either the baseline scores or Δ scores between active and sham sessions. Contrary to expectations, no such relationships were identified (Table 4.6 and 4.7). It is noteworthy, however, that a correlation between baseline measures of SSRT and GABA concentration and GABA and %BOLD in the rIFG, but these relationships failed to survive correction for multiple comparisons and the corresponding BFs were inconclusive.

Table 4.6. Pearson's correlations between *baseline* measures of GABA concentration, %BOLD and behavioural measures of action updating.

DVs		r	*p*	α	BF
GABA	SNS RT	-0.15	.423		0.35
	DNS RT	-0.2	.3		0.43
	SSRT	-0.36	.052		1.41
	DRT1	-0.2	.285		0.43
	DRT2	0.05	.803		0.27
	BOLD (Stop)	-0.39	.035	.0036	1.95
	BOLD (Stop Fix)	-0.29	.121		0.76
	BOLD (Doub)	0.12	.517		0.31
	BOLD (Doub Fix)	0.09	.635		0.29
%BOLD (Stop)	SNS RT	-0.34	.067		0.96
	SSRT	-0.15	.418		0.26
%BOLD (Double)	DNS RT	0.21	.267		0.35
	DRT1	0.21	.259		0.35
	DRT2	-0.01	.969		0.19

Note. **DVs**= dependent variables; **r=**Pearson's correlation coefficient; **p**=p-value; **BF**=Bayes Factor; **SNS RT**= reaction time to stop no-signal trials; **DNS RT**= reaction time to double no-signal trials; **SSRT**= stop signal reaction time; **DRT1=**reaction time of the initial response on double signal trials; **DRT2**= reaction time of the additional response on double signal trials minus the signal onset asynchrony; **%BOLD**= blood oxygen level dependent signal change in the rIFG. %BOLD was extracted from signal>no-signal contrasts in either the SST or DT or from signal>all fixations (**fix**) in either the SST or DT. Note that for any BFs calculated for GABA-related data the prior scale factor was reduced by √2 (see section 4.4.2) All degrees of freedom=28. α calculated as: $\alpha(k)=0.05/(n-k+1)$, where n is the number of comparisons (in this case 14), and k is the rank ordering of p-values from 1 to n.

Table 4.7. Correlations between *cTBS-induced* changes of GABA concentration, %BOLD and behavioural measures of action updating.

DVs		r	*p*	BF
GABA^{+}	SNS RT	-0.13	.505	0.32
	DNS RT	-0.03	.873	0.27
	SSRT	-0.16	.399	0.36
	DRT1	-0.17	.363	0.37
	DRT2^{++}	-0.22	.236	0.47
	BOLD (Stop)	0.23	.214	0.51
	BOLD (Stop Fix)	0.08	.677	0.28
	BOLD (Doub)	0.04	.826	0.27
	BOLD (Doub Fix)	0.04	.822	0.27
%BOLD (Stop)	SNS RT	-0.1	.587	0.22
	SSRT	-0.15	.429	0.26
%BOLD (Double)	DNS RT	0.13	.506	0.24
	DRT1	-0.01	.958	0.2
	DRT2^{++}	0.06	.763	0.2

Note. **DVs**= dependent variables, **r**=Pearson's correlation coefficient; ***p***=*p*-value; **BF**=Bayes Factor; **SNS RT**= reaction time to stop no-signal trials; **DNS RT**= reaction time to double no-signal trials; **SSRT**= stop signal reaction time; **DRT1=**reaction time of the initial response on double signal trials; **DRT2**= reaction time of the additional response on double signal trials minus the signal onset asynchrony; **%BOLD**= blood oxygen level dependent signal change in the rIFG. %BOLD was extracted from signal>no-signal contrasts in either the SST or the DT or from signal>all fixations (**fix**) in either the SST or DT. Note that for any BFs calculated for GABA-related data the prior scale factor was reduced by √2 (see section 4.4.2). $^{+}$= analysis conducted on transformed data; $^{++}$= non-parametric required. All degrees of freedom=28. α level for Holm-Bonferonni comparison not shown as all *p*>.05.

4.5.4. Exploratory analyses.

4.5.4.1. Exploration of the effects of cTBS over time

It was possible that the lack of cTBS-induced effects outlined above may be due to the time-varying influence that cTBS is known to have on neuronal excitability (Huang *et al.*, 2005, 2011). To assess this, repeated measures ANOVA were conducted for each of the DVs with cTBS (active, sham) and time added as factors. Analyses of GABA concentration and %BOLD were explored over 2 time points, whereas those of behavioural measures (SSRT, DRT2, DRT1 and no-signal RTs) were explored over 4 time points. This difference was due to the number of MRS/fMRI/behavioural acquisitions within each session. No significant main effects of cTBS or interaction

effects between cTBS and time were found (Tables 4.8 and 4.9). Significant main effects of time were identified for each of the behavioural measures. However, this is likely due to fatigue effects where all measures were found to steadily increase over time in both the active and sham sessions (Figure 4.11).

Table 4.8. Repeated measures ANOVA as applied to each dependent variable, with cTBS (active vs. sham) and time (number of runs) as factors.

DV	Effect	F	df	*p*	BF
GABA^{++}	cTBS	0.17	(1,19)	.682	0.27
	Time	1.84	(1,19)	.191	0.34
	Interac	0.01	(1,19)	.922	0.29
BOLD (stop) $^{++}$	cTBS	0.07	(1,28)	.801	0.2
	Time	1.18	(1,28)	.287	0.32
	Interac	0.52	(1,28)	.478	0.35
BOLD (double) $^{++}$	cTBS	0.46	(1,28)	.504	0.25
	Time	3.02	(1,28)	.093	0.52
	Interac	2.44	(1,28)	.13	1.06
SSRT	cTBS	0.36	(1,28)	.553	0.17
	Time	**36.18**	(2.35,65.85)	<.001	**1.14^{e+16}**
	Interac	0.89	(2.04,57.02)	.419	0.1
DRT2	cTBS	0.03	(1,28)	.866	0.15
	Time	**7.93**	(1.97,55.2)	<.001	**383.31**
	Interac	0.15	(3,84)	.93	0.05
DRT1	cTBS	0.0002	(1,28)	.988	0.4
	Time	**6.27**	(2.39,66.9)	.002	**11.87**
	Interac	0.48	(3,84)	.7	0.07
SNS RT	cTBS	0.06	(1,28)	.805	0.15
	Time	9.51	(2.18,61)	<.001	**106.68**
	Interac	1.64	(2.27,63.57)	.2	0.11
DNS RT	cTBS	0.0002	(1,28)	.99	0.14
	Time	**11.51**	(1.94,54.29)	<.001	**436.65**
	Interac	0.67	(3,84)	.57	0.07

Note. **DV**= dependent variable; **Effect**=refers to either main effects of cTBS or time or interaction effects (**Interac**); **F**=F-value, significant F-values are reported in bold; **df**=degrees of freedom (Greenhouse-Geisser corrected where applicable – note that df differences between tests are reflective of differences in the missing data points); ***p***=p-value; **BF**=Bayes Factor, BFs>3 are reported in bold; **GABA**= GABA concentration; **BOLD**= blood oxygen level dependent % signal change; **RT**= reaction time; **stop**= stop signal>stop no-signal; **double**= double signal>double no-signal; **SSRT**= stop-signal RT; **DRT2**= RT between onset of additional response and onset of signal in the DT; **DRT1**= reaction time of the initial response on double-signal trials; **SNS**= stop no-signal trials; **DNS**= double no-signal trials; $^{++}$= non-parametric analyses required.

Table 4.9. Pairwise comparisons between behavioural dependent variables and run number.

DV	Comparison	*p*	α	BF
SSRT	1<2	**<.001**	.0125	**1980.57**
	1<3	**<.001**	.0083	**648936.04**
	1<4	**<.001**	.01	**392739.14**
	2<3	**<.001**	.0167	**1500.37**
	2<4	**.003**	.025	**12.44**
	3>4	.467		0.25
DRT2	1<2	**.007**	.01	**6.19**
	1<3	**<.001**	.0083	**198.44**
	1<4	.033		1.69
	2<3	**.012**	.0125	**3.78**
	2<4	.857		0.2
	3>4	.019	.0167	2.64
DRT1	1<2	.014	.01	**3.47**
	1<3	**<.001**	.0083	**28.82**
	1<4	.022		**2.35**
	2<3	.024		2.22
	2<4	.36		0.29
	3>4	.13		0.58
SNS RT	1<2	**.004**	.01	**9.73**
	1<3	**<.001**	.0083	**213.64**
	1<4	**.007**	.0167	**6.33**
	2<3	**.005**	.0125	**8.93**
	2<4	.214		0.41
	3>4	.124		0.6
DNS RT	1<2	**.003**	.01	**12.19**
	1<3	**<.001**	.0083	**171.52**
	1<4	**.005**	.0167	**7.99**
	2<3	**.003**	.0125	**12.07**
	2<4	.3		0.33
	3>4	.6		7.54

Note. Pairwise comparisons conducted for behavioural dependent variables only as no main effect of run number was found for GABA or %BOLD measures (see Table 4.8). **DV**= dependent variable; **Comparison**=run numbers compared (the run for which the DV was greater is indicated by the direction of the greater than symbol); ***p***=*p*-value, *p*-values that survive correction for multiple comparison are reported in bold; **BF**=Bayes Factor, BFs>3 are reported in bold; **SSRT=**stop-signal reaction time; **DRT2**=the duration between the onset of the additional response and the signal onset on double-signal trials; DRT1= the RT of the initial response on double signal trials; SNS RT= RT to stop no-signal trials. α calculated as: $\alpha(k)=0.05/(n-k+1)$, where n is the number of comparisons (in this case 18), and k is the rank ordering of p-values from 1 to n. Correction was conducted separately for each DV.

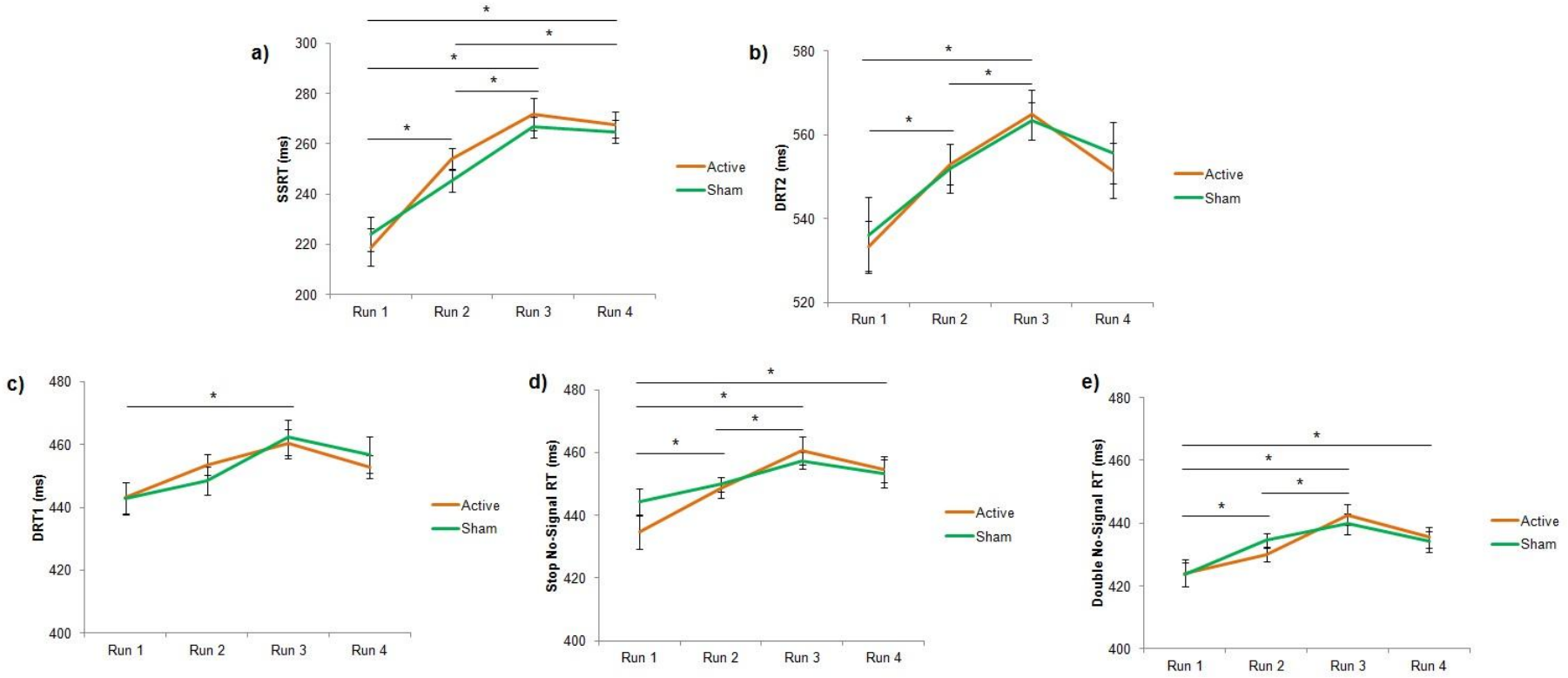


Figure 4.11. Changes across runs in behavioural measures: **(a)** stop signal reaction time (SSRT), **(b)** the latency of the double response (DRT2), **(c)** the latency of the initial response on double signal trials (DRT1), **(d)** the latency of responses to stop no-signal trials, **(e)** the latency of responses to double no-signal trials.

Linear Mixed Effects analyses were also undertaken for behavioural measures using identical procedures as described in Verbruggen *et al.* (2010). Findings were consistent with the ANOVAs reported in Tables 4.8 and 4.9, where time was found to be the only influential factor (APP10.3.6.5.2).

4.5.4.2. The effects of cTBS on remote ROIs

Although largely in the anticipated direction (i.e. BOLD activity suppressed subsequent to active relative to sham cTBS), paired sample t-tests found no evidence for cTBS-induced modulation of %BOLD in ROIs remote to the site of application (Table 4.10).

Table 4.10. Paired sample t-tests exploring the effect of cTBS on BOLD activity within ROIs remote to the site of cTBS application under active vs. sham conditions.

	Stop			Double		
ROI	t	*p*	BF	t	*p*	BF
R pre-SMA	1.83	.077	0.85	-1.26	.216	0.4
R STR	-0.41	.682	0.21	-0.64	.530	0.23
R GPe	-0.42	.677	0.21	-0.27	.787	0.20
R GPi	-0.4	.693	0.21	-0.41	.687	0.21
R STN	-0.53	.598	0.22	-0.6	.552	0.23
R SN	-1.05	.303	0.32	0.44	.66	0.21
R THAL	-0.58	.568	0.23	-1.29	.208	0.41
L pre-SMA	0.48	.636	0.22	-0.93	.362	0.29
L STR	-0.38	.710	0.21	-0.92	.366	0.29
L GPe	-1.44	.162	0.49	-0.87	.393	0.28
L GPi	-1.33	.193	0.43	-0.66	.517	0.24
L STN	-1.18	.249	0.37	-1.27	.552	0.40
L SN	-1.67	.106	0.67	-0.34	.733	0.21
L THAL	-1.14	.262	0.35	-1.66	.109	0.66

Note. Analysis were conducted on %BOLD in each region of interest (**ROI**) acquired from the signal>no-signal contrasts in the SST and DT. **t**=t-value; ***p***=*p*-value; **BF**=Bayes Factor; **R**=right; **L**=left; **pre-SMA**=pre-Supplementary Motor Area; **STR**= striatum; **GPe**= globus pallidus externa; **GPi**= globus pallidus interna; **STN**= subthalamic nucleus; **SN**= substantia nigra; **THAL**= thalamus. Note that for any BFs calculated for GABA-related data the prior scale factor was reduced by √2 (see section 4.4.2). All degrees of freedom=29. α-level for Holm-Bonferonni comparison not shown as all $p>.05$.

4.6. Discussion

The primary aim of the current work was to explore the neurophysiology and neurochemistry of action updating. Of particular interest was whether the principle inhibitory neurotransmitter, GABA, was related to behavioural measures of action updating. If cTBS-induced modulation of GABA and behaviour were found to be related, a potential relationship could have been inferred. Contrary to expectations, no such relationships were found. Furthermore, inconsistent with previous research, cTBS did not exert modulatory effects on local or remote BOLD activity, GABA concentration, or behavioural indices of inhibitory and non-inhibitory action updating. The inter-individual variability in response to non-invasive neurostimulation is well known (e.g. Hamada *et al.*, 2013; López-Alonso, Cheeran, Río-Rodríguez, & Fernández-Del-Olmo, 2014) and may be key to understanding the lack of effects in the current study, but alternative explanations are also possible.

It is probable that the effects of cTBS on BOLD activity and GABA concentration are region-dependent (Stagg *et al.*, 2009). Indeed, previous reports of cTBS-elevated GABA levels in the frontal cortex have been indirect (Dubin *et al.*, 2014), and other work has concentrated on motor and occipital regions (Allen *et al.*, 2014; Stagg *et al.*, 2009). Furthermore, it is possible that the intensity of cTBS applied to the rIFG under active conditions was not sufficient to induce detectable effects, should they exist. Although the mean intensity of cTBS applied here was comparable to that employed by Verbruggen *et al.* (2010; Study 2: 65.23%AdjMT, Verbruggen et al.: 70%AdjMT), the discomfort associated with cTBS to the rIFG rendered the intensity lower than that used in other studies (e.g. 80%MT/80%AdjMT; Allen *et al.*, 2014; Hubl *et al.*, 2008; Stagg *et al.*, 2009[88]).

While BFs indicated evidence in favour of no effect of cTBS on BOLD activity in the rIFG (and remote regions), the evidence for an effect of cTBS on GABA was deemed inconclusive. Speculatively, the uncertainty of cTBS-induced effects on GABA concentration may be in-part associated with the unreliability of spectral quantification in the frontal lobes (owing to the inhomogeneity of magnetic fields in these regions; de Graaf, 2007). This is evidenced by the poor test-retest reliability and high variability in GABA concentrations acquired both within and between sessions (Table 4.4). This

[88] Studies that have found basal ganglia effects of repetitive TMS have also applied TMS at higher intensities (90%-110% MT; Bestmann *et al.*, 2004; Zandbelt *et al.*, 2013).

irregularity may also explain why the evidence for a GABA-SSRT and GABA-BOLD relationship also proved inconclusive. While it is of course possible that GABA is unrelated to these measures, more evidence is required. Future work could explore manual shimming techniques (de Graaf, 2007), acquire MRS spectra at higher magnetic fields (known to improve identification of metabolites in MRS spectra; Mullins, McGonigle, O'Gormon *et al.*, 2014; Puts & Edden, 2012) and include larger samples to overcome such methodological issues[89].

The most surprising result from this study was the absence of cTBS-induced impairments in SSRT and DRT2 as revealed by Verbruggen *et al.* (2010). Although fMRI-guided TMS application has been found to enhance functional relevance of TMS coil placement (Sack, Kadosh, Schuhmann *et al., 2*008), it is unlikely that coil misplacement contributed to the absence of effects here. Not only did I use the same localisation technique as Verbruggen *et al.* (2010), the site of application (*pars opercularis*) was also found to be reliably recruited under both SST and DT conditions in Study 1 as well as in the current study (Figure 4.10). Instead, the difference in testing environments between studies may explain the disparity in findings. Importantly, the current study was carried out in an MR scanner, as opposed to a laboratory as per Verbruggen *et al.* (2010). Differences in behavioural performance (as measured by RT and error rates) have been found between these locations (Koch *et al., 2*003; van Maanen *et al., 2*015; Hommel *et al., 2*012; Koten *et al., 2*013; Assecondi *et al., 2*010). Specifically, van Maanen *et al.* (2015) found decreased attention and slower motor responses in an MR, relative to lab, environment (although note that the extent of this may be task dependent). As such, it is possible that the influence of the MR environment may outweigh cTBS-induced effects rendering them undetectable. This could be easily tested by running a within-subjects study exploring the effects of cTBS on behavioural indices of action updating in the lab vs. MR (mock) environment.

The presence of very subtle effects of cTBS on SSRT may also explain why the results of the Bayesian meta-analysis indicates evidence towards a cTBS-induced disruption of the latency of the stop process - even in the absence of robust effects in the current study. The results from this meta-analysis also indicates evidence towards the null (although still inconclusive) for a cTBS-induced impairment in the latency of

[89] If relationships between dependent measures are robustly observed in future work, moderator and mediator analyses (Baron & Kenny, 1986; Judd *et al.*, 2001) should be incorporated where possible. These analyses would enable the assessment of the interactions between measures and shed light as to the mechanisms by which such relationships are realised.

DRT2. Thus it is possible that the cTBS-induced impairments in DRT2 observed by Verbruggen *et al.* (2010) may have been the result of inadvertent stimulation of the posterior ventral premotor cortex (Aron *et al., 2*014b), an area known to have a strong TMS-induced inhibitory influence over the motor cortex when action plans require reprogramming (Buch *et al.,* 2010). More evidence is required but collectively these results might indicate support for a specialised role of the rIFG in response inhibition. Curiously though, this functional specificity is not reflected in the BOLD data, which demonstrates the *pars opercularis* is recruited in response to both inhibitory and non-inhibitory action updating in the sham cTBS condition (Figure 4.10). As discussed previously, this pattern of activity has been found in other studies employing the SST and DT (Chatham *et al.,* 2012; Erika-Florence *et al., 2*014; Hampshire, 2015; Tabu et*al., 2*011; see also Dodds *et al., 2*011), as well as in Study 1. While this could be representative of difference in response control demands between studies, speculatively, it is also possible that the rIFG may house neurons specialised for both inhibitory and non-inhibitory processes. This is something that could be explored in animal neurophysiology studies, or in humans using TMS-adaptation (a technique that selectively promotes the facilitation of functionally specific neurons enabling us to dissociate them from others in close proximity; Cattaneo, Sandrini, & Schwarzbach, 2010; Cattaneo & Silvanto, 2008; Silvanto, Muggleton, Cowey, & Walsh, 2007; Silvanto, Muggleton, & Walsh, 2008).

Finally, it is also possible that the cTBS-induced effects established by Verbruggen *et al.* (2010) could have been the result of a false positive, or an overestimate of the effect size (Type M error). By pre-registering my design and analyses prior to data collection I may have eliminated subtle forms of research bias that are known to inflate effect size estimates and false discovery rates.

Overall it is clear that more evidence is required before concrete conclusions can be made regarding the role of the rIFG and GABA in supporting action updating. Evidence was indicative of a baseline relationship between GABA and SSRT and GABA and BOLD. Although inconclusive, this suggests potential for response inhibition to be supported by GABA-BOLD coupling in the rIFG. The current study largely failed to replicate the findings of Verbruggen *et al.* (2010; see also Chambers *et al.,* 2006, 2007; Dambacher *et al.,* 2014). However, the meta-analysis suggests evidence in favour of an effect of cTBS on response inhibition, but not in favour of a role in non-inhibitory action updating. It is possible that cTBS-induced effects were not fully

realised due to technical difficulties in applying cTBS to the rIFG, which may be compounded by poor GABA quantification in frontal regions (de Graaf, 2007) and the MR environment itself (van Maanen *et al.*, *2*015).

Chapter 5. Study 2, part II

Replication of Study 1

As discussed in Chapter 1, there have been claims that psychological science is in the midst of a 'reproducibility crisis' (c.f. Anderson *et al.*, 2016; Gilbert et al., 2016) and part of the decision to pre-register the key studies presented within this thesis was to aid transparency as a means to assist future replication attempts. The pathways analyses outlined in Chapter 3 were largely exploratory and were not pre-registered. In acknowledgment of the importance of replication (particularly when using novel analytic techniques such as those employed in Chapter 3) I present an attempt to replicate the fMRI results presented in Chapters 2 and 3. Here, I use fMRI data acquired from the sham sessions in Study 2 to establish whether the pattern of BOLD under the different action updating conditions in both cortical and subcortical regions could be replicated.

It should be noted that the series of analyses presented here do not constitute a direct replication attempt of Study 1 as there are key differences between the methods and analyses employed. For clarity I note that these are: 1) the ignore task (IT) was omitted from Study 2; 2) blocks of the SST and the DT were presented in an interleaved, rather than randomised order as in Study 2; 3) each behavioural run comprised of 6 blocks of each task (12 blocks in total) in Study 2, relative to 3 blocks of each task (9 in total) in Study 1; 4) SSDs/SOAs were adjusted after each behavioural run in Study 2 rather than after every 2nd behavioural run as in Study 1; 5) the use of a spatial smoothing kernel was omitted from the pre-processing of fMRI data in Study 2 (as recommended by de Hollander, *et al.*, 2015; see Section 4.4.1).

5.1. Analyses and results

The analyses concentrate on replicating the 2 most important findings revealed in Study 1. These were: 1) the exclusive recruitment of anterior rIFG under SST conditions, and 2) that response inhibition and response execution were supported by lateralised cortico-subcortical activity. All analyses were conducted on data acquired from the sham cTBS

sessions in Study 2 only. Data screening and analysis methods are reported in Chapters 2 and 3 (Sections 2.3.2., 2.3.2.2. and 2.3.3. 3.2).

5.1. 1. Replication of cortical activity

As per Study 1, data were explored at the whole brain level using signal>no-signal contrasts in the SST and DT. As per Study 1 (Section 2.4.2), a right lateralised network of activity was found to underlie response inhibition and a more bilateral network of activity was found to underlie non-inhibitory action updating (Figure 5.1). Consistent with Study 1, there was a more anterior extension of activity associated with stopping, while activity associated with the DT appeared to be concentrated around motor regions. The general pattern of activity appeared less diffuse in the current study relative to the same contrasts in Study 1 (see Figure 5.1 and 5.2). Such differences are likely to be due to the omission of a spatial smoothing kernel in the current study (relative to the 5mm FWHM Gaussian kernel used in Study 1; Figure 5.2). Additionally, a reduction in DLPFC and ACC activity was observed in the current study relative to Study 1. It is unlikely that this is caused by a difference in error rates as stop-signal success was comparable across studies ($t_{(56.58)}$=0.43, *p*=.671, BF=0.28). It is probable that these differences are the result of the omission of the spatial smoothing kernel (de Hollander *et al., 2*015; Kamitani & Sawahata, 2010; Mikl, Marečeck, Hluštík *et al.*, 2008; Triantafyllou, Hoge, & Wald, 2006) and the decreased working memory demands (Crone *et al., 2*006; Mostofsky *et al.*, 2003; Simmonds *et al.*, 2008; see D'Esposito *et al., 2*000 for a review) given the exclusion of the IT from the current study. The interleaved SST and DT blocks in a predictable order is also likely to have contributed to this.

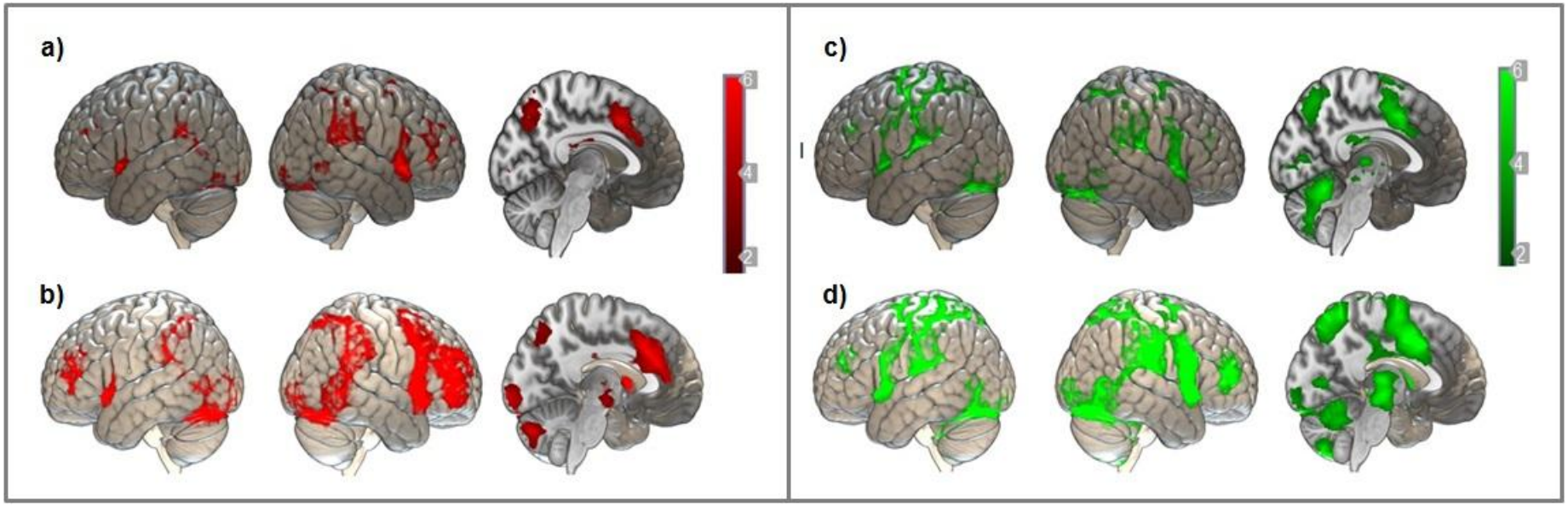


Figure 5.1. Whole brain BOLD activity under inhibitory (red) and non-inhibitory action updating (green) conditions from Studies 1 and 2. Activation patterns yielded from the signal>no-signal contrasts in the SST **(a)** and **(b)** and DT **(c)** and **(d)**. Panels **(a)** and **(c)** illustrate the results from Study 2, and the panels **(b)** and **(d)** illustrate the results from Study1. Clusters are significant at Z>2.3, p<.05. Scales correspond to the Z-value within active regions. It is clear that the omission of the spatial smoothing kernel in Study 2 has reduced the anterior spread of activity across both SST and DT conditions. Images presented in neurological format (L=L; R=R).

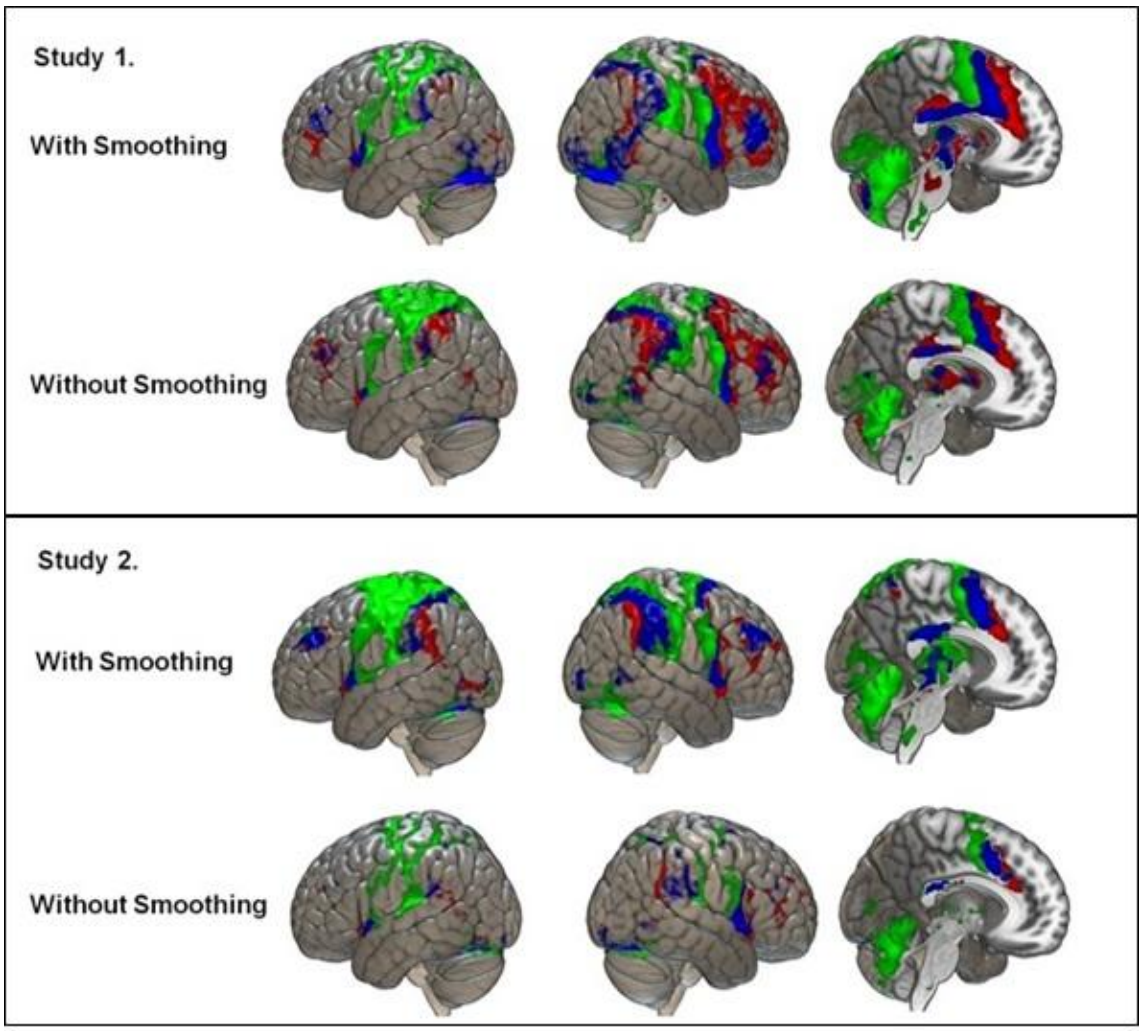


Figure 5.2. Comparison of the spatial distribution of activity when data from Study 1 (top panel) and Study 2 (bottom panel) were pre-processed with 5mm FWHM spatial smoothing kernel. Images depict common and distinct regions of actvtiy associated with different forms of action updating. Cluster based activity significant at Z>2.3, *p*<.05. Images are illustrated in neurological format (L=L; R=R). Regions unique to inhibitory action updating (stop signal > stop no-signal) after disjunction of voxels activated with non-inhibitory action updating (double signal > double no-signal) are shown in red. Regions specific to non-inhibitory action updating after disjunction of voxels activated with inhibitory action updating are shown in green. Activtiy common to both inhibitory and non-inhibitory action updating are shown in blue. The images show that the addition of spatial smoothing leads to more widespread activity under all conditions, which can be clearly observed in right frontal and medial frontal regions.

As per Study 1, disjunction analyses revealed unique anterior rIFG recruitment (i.e. the *pars triangularis*) under SST, relative to DT conditions (Figure 5.3, Table 5.1). Of importance, is the large percentage of exclusivity of the *pars opercularis* (41.19%) recruited under SST conditions (Table 5.1). Crucially, this region includes the coordinates of the specialised inhibitory module posit by Aron *et al*. (2014a; MNI=48, 16, 18). However, while the recruitment of the rIFG (and its sub-divisions) were

generally greater in the SST relative to the DT, this difference was not reliable (rIFG: $t_{(29)}$=1.61, *p*=.119, BF=0.61; *pars opercularis*: $t_{(29)}$=1.71, *p*=.098, BF=0.71; *pars triangularis*: $t_{(29)}$=1.04, *p*=.308, BF= 0.32). Additionally, differential pre-SMA activity between contexts was not conclusively observed ($t_{(29)}$=2.42, $p_{.0125}$=.022, BF=2.34). Right-lateralised fronto-parietal activity was found to be common to both inhibitory and non-inhibitory action-updating requirements as per Study 1 (Figure 5.3, Table 5.1).

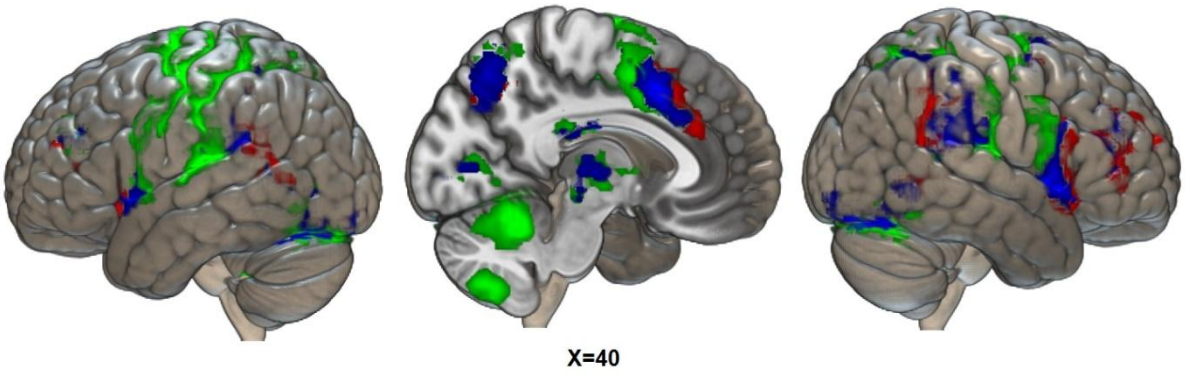


Figure 5.3. Common and distinct regions of activity associated with different forms of action updating. Regions unique to inhibitory action updating subsequent to disjunction analysis are shown in red. Regions unique to non-inhibitory action updating subsequent to disjunction analysis are shown in green. Regions of activity common to both inhibitory and non-inhibitory action updating as revealed by conjunction analysis are shown in blue. All activated region exceed Z>2.3, *p*<.05. Images presented in neurological format (L=L, R=R).

Table 5.1. The number of voxels and % of ROI recruited under different updating conditions as revealed by disjunction and conjunction analyses.

Analysis	ROI	#	%	Z	MNI
(a) Exclusively inhibitory	rIFG	392	31.31	4.60	19,71,39
Disjunction: (stop signal>stop no-signal) -	Pars op	285	41.19	4.60	19,71,39
(double signal> double no-signal)	Pars tri	90	17.93	4.4	20,74,34
	pre-SMA	82	3.44	4.23	42,73,58
(b) Exclusively non-inhibitory	rIFG	3	0.24	2.82	18,70,52
Disjunction: (double signal>double no-signal) -	Pars op	3	0.43	2.82	18,70,52
(stop signal>stop no-signal)	Pars tri	0	0	N/A	N/A
	pre-SMA	539	22.59	6.71	45,64,61
(c) General updating	rIFG	374	29.87	4.89	18,68,43
Conjunction: (stop signal>stop no-signal) ∩	Pars op	358	51.73	4.89	18,68,43
(double signal>double no-signal)	Pars tri	15	2.99	2.95	20,73,36
	pre-SMA	432	18.12	4.79	44,69,58

Note. Clusters of activity exceeded Z>2.3, $p<.05$. **ROI**=region of interest; **#**=number of voxels with ROI activated; **%**= percent of ROI activated; **Z**=maximum Z-value within ROI; **MNI**=coordinates corresponding to maximum Z-value in standard space.

5.1. 2. Pathways analyses

Analyses were conducted to assess whether activity in cortical and subcortical regions was consistent with the putative pathways outlined in Chapter 3. All analyses were computed as outlined in Sections 3.2 and aimed to: 1) assess the general consistency between the data and the pathways models; 2) assess the spatial distribution of activity under conditions of response execution and response inhibition and 3) explore the interrelations amongst regions found to be de/activated to a significant extent under differential response control conditions.

Compound contrasts were computed and the mean %BOLD within ROIs extracted using Featquery. Due to the omission of the IT in the current study, 104 contrast combinations were computed (as opposed to the 203 computed in Chapter 3). Contrasts were categorised exactly as per Study 1 as either reflective of response execution or response inhibition, with the latter further divided into proactive and reactive contrasts (see APP10.4.2).

5.1. 2.1. Replication of modelling analyses

%BOLD data for each ROI (bilateral) were multiplied by the anticipated activations (+1) and deactivations (-1) reflective of the direct, indirect and hyperdirect pathways as per Table 3.9. Model fits were assessed by a series of one-tailed t-tests.

Results were not in agreement with the findings presented in Study 1. The pattern of activity acquired from categorised contrasts was inconsistent with the models they were expected to represent (Table 5.2). All BFs were <1/3 with the exception of those corresponding to the direct pathway which were found to be inconclusive. Furthermore, when the data were fit to the incorrect models (Table 5.3), data corresponding to response execution was found to fit well (although BFs were inconclusive), although contrasts corresponding to response inhibition were inconsistent with the pattern anticipated for the direct pathway. The reasons for the discrepancies between studies are possibly due to the methodological differences between tasks, including the omission of the smoothing kernel and the IT in the current study. The role of the IT is discussed later.

Table 5.2. Summary of one-tailed t-tests and Bayesian equivalents of the fit between %BOLD averaged across each category for each ROI and the models used to represent each pathway.

Pathway		t	df	*p*	BF	JZS
Direct		1.71	29	.049	0.94	0.71
Indirect	Proactive	-0.52	29	.698	0.11	0.22
	Reactive	0.62	29	.271	0.19	0.19
	All	0.11	29	.458	0.15	0.2
Hyperdirect	Proactive	-0.52	29	.698	0.19	0.22
	Reactive	0.37	29	.356	0.2	0.21
	All	0.28	29	.390	0.21	0.2

Note. **t**=t-value; **df**= degrees of freedom; **BF**=Bayes Factor; **JZS**=model fits using JZS prior; **Proactive**= contrasts categorised as proactive inhibition; **Reactive**= contrasts categorised as reactive inhibition; **All**= all contrasts categorised as inhibition regardless of whether proactive or reactive.

Table 5.3. Summary of one-tailed t-tests and Bayesian equivalents of the fit between %BOLD averaged across each category for each ROI and the inappropriate models.

Pathway	t	df	*p*	BF	JZS
Direct	-1.53	29	.932	0.04	0.56
Indirect	2.13	29	.021	2.1	1.38
Hyperdirect	1.52	29	.069	0.96	0.55

Note. Here, all contrasts categorised as response inhibition were fit to the direct pathway model, whilst all contrasts categorised as response execution were fit to the indirect and hyperdirect pathway models. **t**=t-value; **df**= degrees of freedom; **BF**=Bayes Factor; **JZS**=BFs using JZS prior.

5.1.2.2. Replication of the lateralised distribution and interrelations between ROIs

As per Study 1, I explored the lateralised pattern of activity within the BG and THAL of the previously described pathways, as well as how they might extend to the highlighted cortical regions of interest (preSMA and IFG). An initial 3-way ANOVA comprised of condition (execution vs. inhibition) and site (8 levels, representation of each subcortical and cortical ROI) and hemisphere (left vs, right) as factors was applied to the raw %BOLD data. As per Study 1, a significant 3-way interaction was found ($F_{(2,203)}$=4.4, p<.001)indicating that right and left ROIs were recruited to differently under different response control conditions. Importantly, the significant interaction between condition

and hemisphere persisted ($F_{(1,29)}$=2.27, p=.031)[90]. The presence of the interaction effect warranted further investigation using simple effects analysis (Table 5.4). As per Study 1, these were followed by a series of moderator/mediator analyses (Baron & Kenny, 1986; Judd *et al.*, 2001) to assess the interrelations between ROIs. To clarify, in Frequentist statistics a covariate has a mediating influence on the relationship between two other variables if its incorporation eliminates the significance of the original relationship. If this significant relationship is reduced but not eliminated, the covariate can be described as having moderating influence on the original relationship. For Bayesian equivalents, moderating relationships were indexed by a reduction in the BF from >3 to BF<3, but greater than 1/3. A mediating relationship was indexed by a reduction in the BF from BF>3 to BF<1/3.

Consistent with the findings from Study 1, activity under conditions of response execution and response inhibition appeared to be lateralised to the left and right hemispheres, respectively (Table 5.4; Figure 5.4). However, the general expanse of activity amongst ROIs was found to differ from that of Study 1. Under conditions of response execution, there appeared to be additional ROIs significantly recruited within both hemispheres. Furthermore, interrelations between ROIs were not restricted to the left hemisphere as per Study 1 and were demonstrated between left and right hemisphere ROIs. Mutual dependence between these ROIs under conditions of response execution was also found (Table 5.5). Conversely, under conditions of response inhibition, activity was limited to cortical structures in the right hemisphere and did not extend to subcortical ROIs as found in Study 1 (Table 5.6; Figure 5.4).

[90] The main effect of condition was observed as in Study 1 ($F_{(1,29)}$=4.92, p=.035), but there was no main effect of site ($F_{(7,203)}$=.64, p=.719) or hemisphere ($F_{(1,29)}$=2.1, p=.158). While the interaction between hemisphere and site was also found in the current study ($F_{(7,203)}$=2.27, p=.031), there was no significant interaction between condition and site observed ($F_{(7,203)}$=1.23, p=.289).

Table 5.4. One-tailed simple effects analyses exploring the spatial distribution of cortical, basal ganglia and thalamic activity under different response conditions.

		Execution vs. Inhibition			Execution			Inhibition		
Hem	ROI	t	*p*	BF	t	*p*	BF	t	*p*	BF
Left	pre-SMA	**3.35**	.001	**24.98**	**2.98**	.006	**7.14**	**-2.84**	.008	**5.37**
	IFG	1.17	.25	0.36	1.05	.304	0.32	-0.98	.337	0.3
	STR	**3.85**	<.001	**55.64**	**4.66**	<.001	**378.95**	-1.85	.075	0.87
	GPe	**2.43**	0.022	2.37	**3.09**	.004	**9.11**	-0.66	.517	0.24
	GPi	1.69	.102	0.69	**2.49**	.019	2.63	0.02	.984	0.19
	SN	**2.35**	0.026	2.03	**2.66**	.013	**3.73**	-0.822	.418	0.27
	STN	0.15	.88	0.2	0.73	.472	0.248	0.49	.628	0.22
	THAL	**4.39**	<.001	**195.52**	**5.61**	<.001	**4.26^{e+03}**	-1.46	.156	0.5
Right	pre-SMA	-0.11	.91	0.2	**2.14**	.041	1.41	**3.27**	.003	**13.48**
	IFG	**-2.26**	.031	1.75	0.12	.903	0.2	**4.46**	<.001	**231.21**
	STR	**2.2**	.036	1.55	**3.47**	.002	**21.47**	0.41	.689	0.21
	GPe	1.43	.163	0.49	**2.43**	.021	2.39	0.24	.815	0.2
	GPi	0.08	.937	0.2	0.85	.401	0.27	1.1	.279	0.34
	SN	0.93	.358	0.29	**2.32**	.028	1.93	0.97	.342	0.3
	STN	1.62	.116	0.63	1.79	.084	0.8	-0.87	.393	0.28
	THAL	**2.06**	.049	1.22	**3.63**	.001	**31.19**	0.62	.537	0.23

Note**.** Analyses were conducted separately for each region of interest (**ROI**) when responses were to be executed, or inhibited, or compared. **Hem**=hemisphere; **ROI**= region of interest; **t**=t-value, significant t-values are reported in bold; ***p***=*p*-value; **BF**=Bayes Factors, BFs>3 are reported in bold; **pre-SMA**=pre-supplementary motor area; **IFG**=inferior frontal gyrus; **STR**=striatum; **GPe**=globus pallidus externa; **GPi**=globus pallidus interna; **STN**=subthalamic nucleus; **SN**=substantia nigra; **THAL**=thalamus. All degrees of freedom=29. All significant t-values and BFs>3 are shown in bold.

Table 5.5. The moderating and mediating effects of the addition of covariates under conditions of response execution.

			Left						Right				
Hem	ROI	Original	pre-SMA	STR	GPe	GPi	SN	THAL	pre-SMA	STR	GPe	SN	THAL
Left	pre-SMA	.006		.939	.139	.023	.067	.677	.066	.491	.071	.219	.499
		7.14		**0.2**	**0.56**	**N/A**	**0.97**	**0.21**	**N/A**	**.25**	**N/A**	**N/A**	**0.25**
	STR	<.001	.005		.006	.001	.002	.67	.001	<.001	.001	.001	.023
		378.95	**8.83**		**6.97**	**N/A**	**19.12**	**0.22**	**N/A**	**71.67**	**N/A**	**N/A**	**2.29**
	GPe	.004	.101	.977		.09	.071	.464	.046	.239	.096	.057	.412
		9.11	**0.70**	**0.2**		**N/A**	**0.93**	**0.25**	**N/A**	**0.38**	**N/A**	**N/A**	**0.27**
	GPi	.019	.078	.308	.556		.07	.668	.076	.077	.061	.089	.181
		N/A	**N/A**	**N/A**	**N/A**		**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**
	SN	.013	.153	.578	.227	.046		.695	.113	.169	.137	.112	.695
		3.73	**0.52**	**0.23**	**0.39**	**N/A**		**0.21**	**N/A**	**0.48**	**N/A**	**N/A**	**0.21**
	THAL	<.001	<.001	.025	<.001	<.001	<.001		<.001	<.001	<.001	<.001	<.001
		4.26E+03	**96.99**	**2.14**	**91.11**	**N/A**	**180.4**		**N/A**	**65.89**	**N/A**	**N/A**	**513.31**
Right	pre-SMA	.041	.783	.523	.669	.171	.467	.125		.916	.372	.148	.584
		N/A	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**		**N/A**	**N/A**	**N/A**	**N/A**
	STR	.002	.011	.01	.077	.007	.02	.207	.019		.028	.016	.425
		21.47	**0.71**	**4.54**	**0.86**	**N/A**	**2.59**	**0.42**	**N/A**		**N/A**	**N/A**	**0.27**
	GPe	.021	.311	.856	.822	.069	.255	.687	.172	.555		.187	.601
		N/A	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**		**N/A**	**N/A**
	SN	.028	.107	.757	.488	.132	.275	.727	.098	.347	.251		.632
		N/A	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**
	THAL	.001	.064	.701	.075	.009	.035	.01	.01	.238	.019	.015	
		31.19	**1**	**0.21**	**0.88**	**N/A**	**1.62**	**4.57**	**N/A**	**0.38**	**N/A**	**N/A**	

Note. BFs are shown in bold below the corresponding *p*-value. The original values correspond to those yielded from the simple effects analysis (Table 5.4). The table can be read from left to right, where the regions of interest in each column are the covariate added to the moderator/mediator analyses. Hem= hemisphere; **pre-SMA**=pre-supplementary motor area, **STR**=striatum, **GPe**=globus pallidus externa, **GPi**= globus pallidus interna, **SN**= substantia nigra, **THAL**=thalamus, **N/A**= no corresponding BF as criteria of BF>3 not met via simple effects analyses. Values highlighted in blue represent instances of moderation, where the significance of the *p*-value after addition of a covariate is reduced (i.e. *p*-value increased) but the significance remains (i.e. *p*<.05; for Bayesian equivalent, BF<3, but >1/3). Values

highlighted in orange represent instances of mediation, where the *p*-value is increased to >.05 after addition of the covariate (i.e. no longer significant; for Bayesian equivalent, BF<1/3).

Table 5.6. The moderating and mediating effects of the addition of covariates under conditions of response inhibition.

			Left	Right	
Hem	ROI	Original	pre-SMA	pre-SMA	IFG
Left	pre-SMA	.008		<.001	<.001
		5.37		**7.34^{e+04}**	**245.03**
Right	pre-SMA	.003	<.001		.63
		13.48	**1.81^{e+05}**		**0.22**
	IFG	<.001	<.001	.015	
		231.21	**9.45^{e+03}**	**3.33**	

Note. BFs are shown in bold below the corresponding *p*-value. The original values correspond to those yielded from the simple effects analysis (Table 5.4). The table can be read from left to right, where the regions of interest (ROI) in each column are the covariate added to the moderator/mediator analyses. **Hem**=hemisphere; **pre-SMA**=pre-supplementary motor area; **IFG**-inferior frontal gyrus. Values highlighted in blue represent instances of moderation, where the significance of the *p*-value after addition of a covariate is reduced (i.e. *p*-value increased) but the significance remains (i.e. *p*<.05; for Bayesian equivalent, BF<3, but >1/3). Values highlighted in orange represent instances of mediation, where the *p*-value is increased to >.05 after addition of the covariate (i.e. no longer significant; for Bayesian equivalent, BF<1/3).

The inconsistency in the patterns of activity between Study 1 and the current study is likely associated with the omission of the IT. This omission reduced the number of contrast computed (104 in the current study vs. 203 in Study 1) for each response control category – i.e. response execution and response inhibiton (and divisions of proactive and reactive inhibition) and likely led to covariance differences between contrasts within categories between Study 1 and the current study. In Study 1, contrasts including IT events were generally categorised as representative of response execution (Table 3.8). Separation of the activity in response execution contrasts in Study 1 into those related to the IT and DT was found to yield a smaller %BOLD associated with the former, relative to the latter (Figure 5.5). This difference is likely due to the absence of action updating demands in the IT, coupled with the execution of an additional response in the DT. Thus, the presence of the IT 'diluted' the mean %BOLD associated with response execution (Figure 5.5a and 5.5b). Thus in the absence of the IT in the current study, the %BOLD associated with response execution is likely elevated. Conversely, under conditions of response inhibition, contrasts containing IT events provided

additional baseline options in Study 1 (Table 3.8). The disparity between contrasting SST events with IT events (e.g. stop-signal > ignore-signal) was found to be greater than that between SST events and DT events (e.g. stop-signal > double-signal; Figure 5.5c and 5.5d). Therefore, the exclusion of the IT in the current study is likely associated with the reduction in mean %BOLD associated with response inhibition and may explain why subcortical structures were not found to be recruited to a significant extent (Table 5.4; see also Figure 5.4).

These interpretations are supported by the reversal of the %BOLD pattern under conditions of response execution and response inhibition between the studies. In Study 1, activity associated with response inhibition was generally greater than that associated with response execution across ROIs. The opposite was found in the current study, where activity associated with response execution was generally greater than that associated with response inhibition (Figure 5.4). Furthermore, I explored the pattern of activity yielded in Study 1 after exclusion of contrasts containing IT events (APP10.4.2.2). Crucially, the interrelations between ROIs (within and between hemispheres) were greater under conditions of response execution.

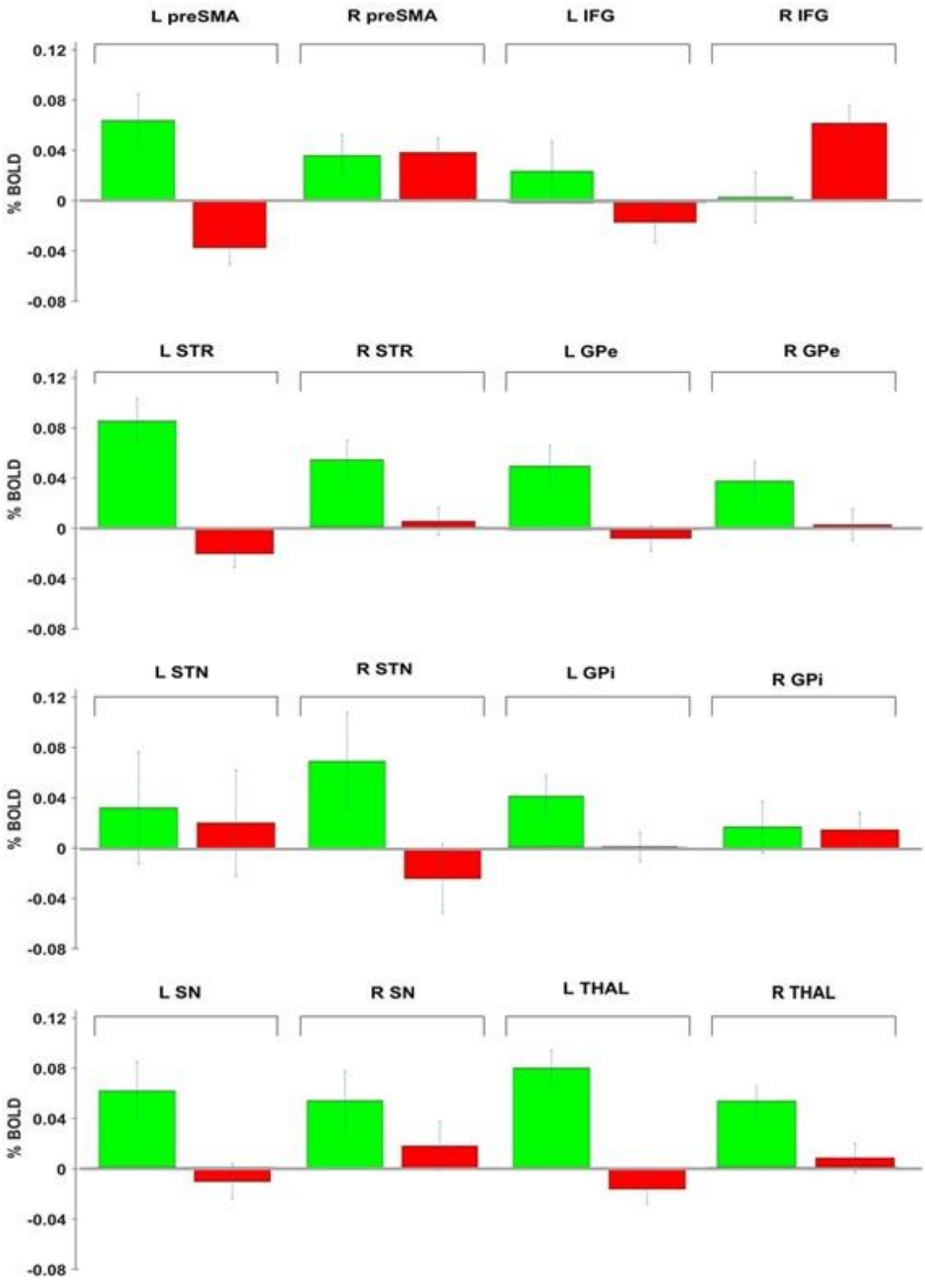


Figure 5.4. The change in %BOLD in under conditions of response execution (green) and response inhibition (red) in left (**L**) and right (**R**) ROIs. The general trend of activity is suggestive of increased recruitment of bilateral ROIs under conditions of response execution relative to response inhibition. This trend opposes that found in Study 1 (see Figure 3.3). **pre-SMA**= pre-supplementary motor area; **IFG**= inferior frontal gyrus; **STR**= striatum; **GPe**= globus pallidus externa; **STN**=subthalamic nucleus; **SN**=substantia nigra; **GPi**= globus pallidus interna; **THAL**= thalamus. Error bars are ± 1 standard error.

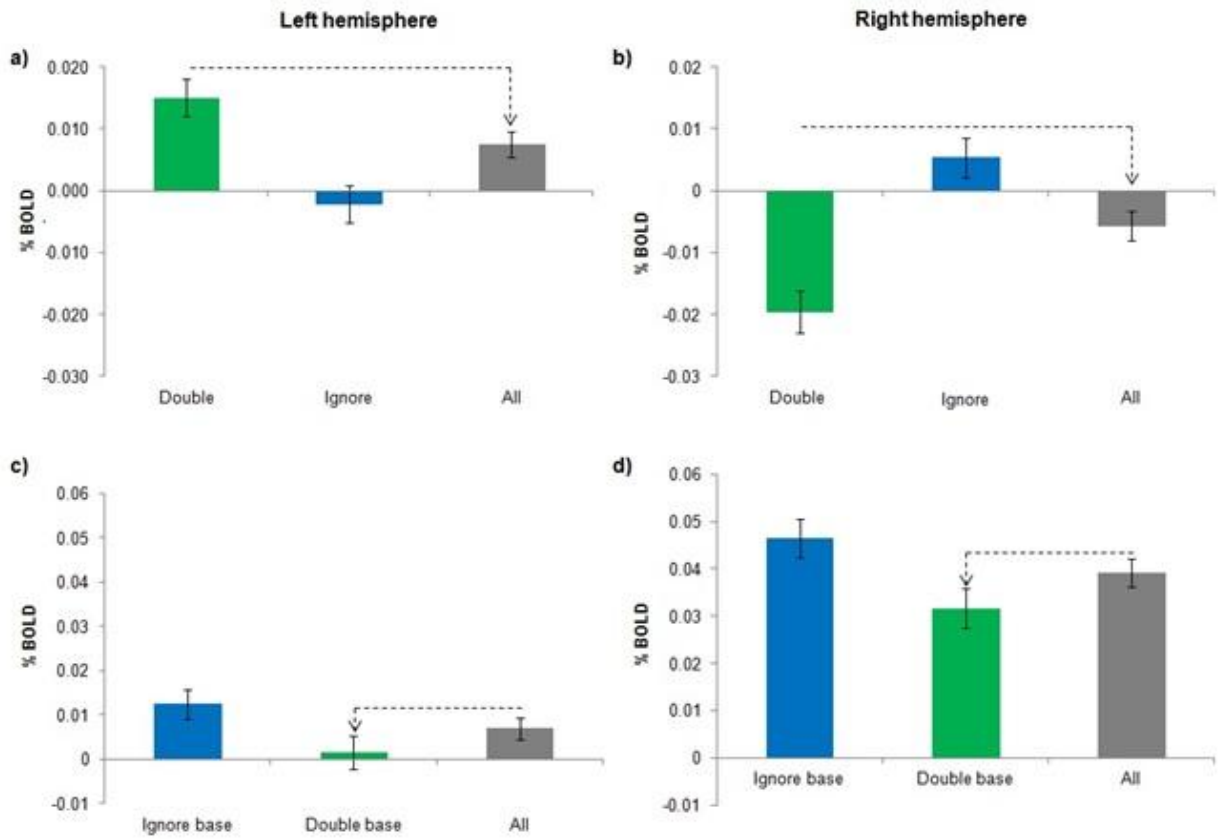


Figure 5.5. The change in %BOLD in Study 1 after exclusion of the ignore-related contrasts. %BOLD was collapsed across all ROIs in either the left or right hemispheres. **(a)** and **(b)** represent changes in response execution contrasts. Overall (All) mean %BOLD was reduced relative to double-related contrasts after ignore contrast exclusion. **(c)** and **(d)** represent changes in response inhibition contrasts. Overall (all) mean %BOLD was reduced when only double-related contrasts were included in the analyses and the ignore-related contrasts excluded. The important changes in mean %BOLD are depicted by the dashed arrows. Error bars show ± standard error.

5.2. Discussion

The aim of this Chapter was to establish whether it was possible to replicate the pattern of BOLD activity under conditions of response execution and response inhibition as revealed Study 1 (N=30 in both studies). The characteristic right-lateralised activity associated with response inhibition (e.g. Aron *et al.*, 2007; Aron & Poldrack, 2006; Cai & Leung, 2011; Kenner *et al.*, 2010; see reviews: Aron, 2007, 2011; Banich & Depue, 2015) and the bilateral activity associated with dual-task demands (e.g. Collette *et al.*, *2*005; Dux *et al.*, 2006, 2009; Erickson *et al.*, *2*005; Heekeren *et al.*, 2006; Tombu *et al.*, *2*011) was observed. Common activity, representative of general action updating demands was identified in fronto-parietal regions, particularly in the right *pars opercularis* and the pre-SMA. However, it is clear that activity within the *pars opercularis* was also uniquely recruited to a greater spatial extent than in Study 1 (Study 1=12.72% with the application of a spatial smoothing kernel, Study 2= 41.19% without smoothing kernel (see Figure 5.1 and 5.2 and Tables 2.2 and 5.1). Furthermore, the specific coordinates of the unique inhibitory module provided by Aron *et al.* (2014b, MNI=48, 16, 18) was found to be active under SST relative to DT conditions in Study 2, but under both conditions in Study 1. Thus it is possible that the smoothing kernel blurred activity from neighbouring regions, ultimately distorting the true extent of rIFG activity under different response control conditions. A review of the studies that had found overlapping activity in the vicinity of the rIFG under SST and DT conditions, revealed that they had used spatial smoothing kernels equivalent to and greater than that used in Study 1 (Study 1: 5mm FWHM; Chatham *et al.*, *2*012: 5mm FWHM; Dodds *et al.*, *2*011: 6mm FWHM; Erika-Florence *et al.*, *2*014: 8mm FWHM; Hampshire *et al.*, *2*010: 8mm FWHM; Hampshire, 2015: 8mm FWHM) and this might have led to misguided conclusions. The omission of spatial smoothing likely contributed to the reduction in *pars triangularis* activity under SST conditions in Study 2, relative to Study 1 (Study 1: 69.32%, Study 2: 17.93%). However, this region was still activated exclusively under SST conditions, with 0 voxels uniquely recruited under DT conditions and minimal recruitment common to both inhibitory and non-inhibitory action updating requirements (2.99%). To fully ascertain the influence of the smoothing kernel on the pattern of rIFG activity, results would need to be compared after analysis with and without the use of a spatial smoothing kernel.

The exclusion of the smoothing kernel is also likely to have contributed to the absence of subcortical effects under conditions of response inhibition; particularly in regions of close proximity, such as the STN and SN (see de Hollander *et al.*, 2015). However, the omission of the IT in the current study is likely to have had a more pronounced effect due to the compound contrast approach employed. As mentioned, the presence of the IT-related contrasts in Study 1 increased the mean %BOLD associated with response inhibition (relative to when contrasted against DT-related events) because the IT offers a baseline free of updating requirements. The difference in inferences that can be made regarding underlying activity is known to be baseline dependent (Mostofsky & Simmonds, 2008; Welvaert & Rosseel, 2013) and as noted in the methods (Section 4.4.1) was a motivator for choosing multiple baseline options for the BOLD/GABA correlations in Study 2. The rIFG and pre-SMA activity probably persisted due to the large associated effect sizes (see Figure 3.3 and Figure 5.4).

Conversely, under conditions of response execution, IT contrasts were largely categorised as reflective of response execution (due to the requirement to make a response on all trials). In Study 1, this was found to have reduced the mean %BOLD when considered across all contrasts and ROIs relative to those associated with the DT only. Again, this is most likely due to the absence of updating requirements in the IT. As mentioned, this interpretation of the disparity between Study 1 and the current work is also evidenced by increased activity under conditions of response execution relative to response inhibition across ROIs (Figure 5.4) and the opposing pattern established in Study 1 (Figure 3.3) as well as the adjusted patterns of activity established in Study 1 after the exclusion of IT contrasts (APP10.4.2.2).

Collectively, these results demonstrate part-replication of the pathways analyses presented in Chapter 3. Lateralisation of both cortical and subcortical activity was largely consistent with that observed in Study 1. However, the increase in interrelations between ROIs under conditions of response execution, and the loss of significant subcortical activity under conditions of response inhibition highlight important methodological considerations that must be made in response control research. Indeed, null effects or discrepancies between findings in previous studies may be due to differences in baselines used for comparison (Mostofsky & Simmonds, 2008; Welvaert & Rosseel, 2013). Furthermore, this work emphasises the importance of pre-registration as it demonstrates the variability of observed results following slight adjustments in task and analysis parameters.

In spite of these methodological variations, this study provided new insights into how the *pars opercularis* could support inhibitory action updating. The omission of the smoothing kernel indicated that nearly half of this region was activated by response inhibition requirements. However, further work is needed to establish the true influence of the spatial smoothing kernel on inferences of rIFG recruitment. Additionally, it remains to be seen if this differentiation replicates. The unique activity associated with response inhibition in the *pars triangularis* persisted in the current study. However, as discussed in Chapter 2, it is not clear whether this pattern reflects the activity of a specific inhibitory module within anterior rIFG or whether it is associated with differences in response control demands required in the SST and DT. This possibility is explored further in Chapter 6.

Chapter 6. Study 3

Dissociable control demands in the context-cueing paradigm

6.1. Overview

The overarching aim of this thesis is to establish whether response inhibition is supported by a specific inhibitory network or by a more generalised system involved in processes common to multiple forms of action updating. In Studies 1 and 2, the neuroanatomical distribution of inhibitory and non-inhibitory action updating was revealed by the combination of functional magnetic resonance imaging (fMRI) and a modified version of Verbruggen *et al*.'s (2010) context-cueing paradigm. Importantly the results suggest a functional disparity in the recruitment of the rIFG under different action updating requirements. Specifically, the anterior *pars opercularis* and the *pars triangularis* was found to be exclusively activated under conditions of response inhibition (see Figure 6.1 for a relevant summary of findings from Study 1), whereas the posterior *pars opercularis* was found to be recruited in response to both inhibitory and non-inhibitory action updating demands[91]. Although this division may reflect a functional dissociation within the rIFG, such interpretations are at odds with recent work employing similar paradigms; where it has been argued that rIFG activity is associated with response control (Dodds *et al.*, 2011) and context-monitoring (e.g. Chatham *et al.* 2012) processes or part of a broader range of cognitive functions that are not necessarily inhibitory (Erika-Florence *et al.*, 2014; Hampshire, 2015; Hampshire & Sharp, 2015a, 2015b). Here, I explore the possibility that the observed rIFG division may reflect different attentional and cognitive demands associated with the sub-tasks comprising the context-cueing paradigm. If such demands are greater for the SST relative to the DT or the IT, this might account for activity in the rIFG, and lead us to question whether this region hosts a specialised inhibitory function.

I begin with an overview of evidence from Studies 1 and 2 that support the possibility that the SST is more cognitively demanding than the DT or the IT, before reviewing additional evidence from the literature. I then adopt a multi-stage analytic approach, examining both psycho-physiological and self-report measures to establish

[91] Note, the findings from Study 2 indicate the posterior portion of the *pars opercularis* to be associated with both inhibitory and non-inhibitory action updating, but the more anterior portion (and leading into the *pars triangularis*) was associated with response inhibition only.

whether there are differences in control demands between the tasks. Even though measurements of the demands would need to be correlated with BOLD activity under different response control conditions to make firm inferences, the work in the current chapter may provide important insights into how well the task demands are matched between the tasks comprising the context-cueing paradigm.

6.2.1. Support from Studies 1 and 2

The potential for rIFG specialisation for response inhibition is supported by multiple studies (see Aron *et al.*, 2014a for a review). However, previous work has indicated that response control demands that are not necessarily inhibitory (e.g. Dodds *et al.*, 2011) may account for these observations. Indeed, increased demands in the SST, relative to the DT or the IT may be evident in both behavioural measures of task performance and unique regions of activity uncovered in Studies 1 and 2 (i.e. the initial fMRI study and the combined fMRI/MRS/TMS study). Relevant findings are illustrated in Figure 6.1.

Performance in the SST can be conceptualised as a race between the stop and go processes. Whether response inhibition is successful or not depends on which process 'wins' this race (Logan & Cowan, 1984). Crucially, the delay between stimulus and signal onsets in the SST are dynamically altered to ensure participants successfully withhold their responses on approximately 50% of signal trials; representative of the theoretical optimum point of competition between the stop and go processes (Logan & Cowan, 1984; Verbruggen & Logan, 2008). Conversely, accuracy on signal trials in the DT and IT are much higher (see Figure 6.1a). It is therefore possible that the difference in rIFG recruitment between task contexts may be driven by the disparity in error rates between them. Indeed, practice of the SST has been found to reduce rIFG recruitment over time (Berkman, Kahn, & Merchant, 2014; Erika-Florence *et al.*, 2014). Furthermore, the ACC and DLPFC are hypothesised to be associated with error detection and performance monitoring and were uniquely recruited under SST conditions (Figure 6.1g, h).

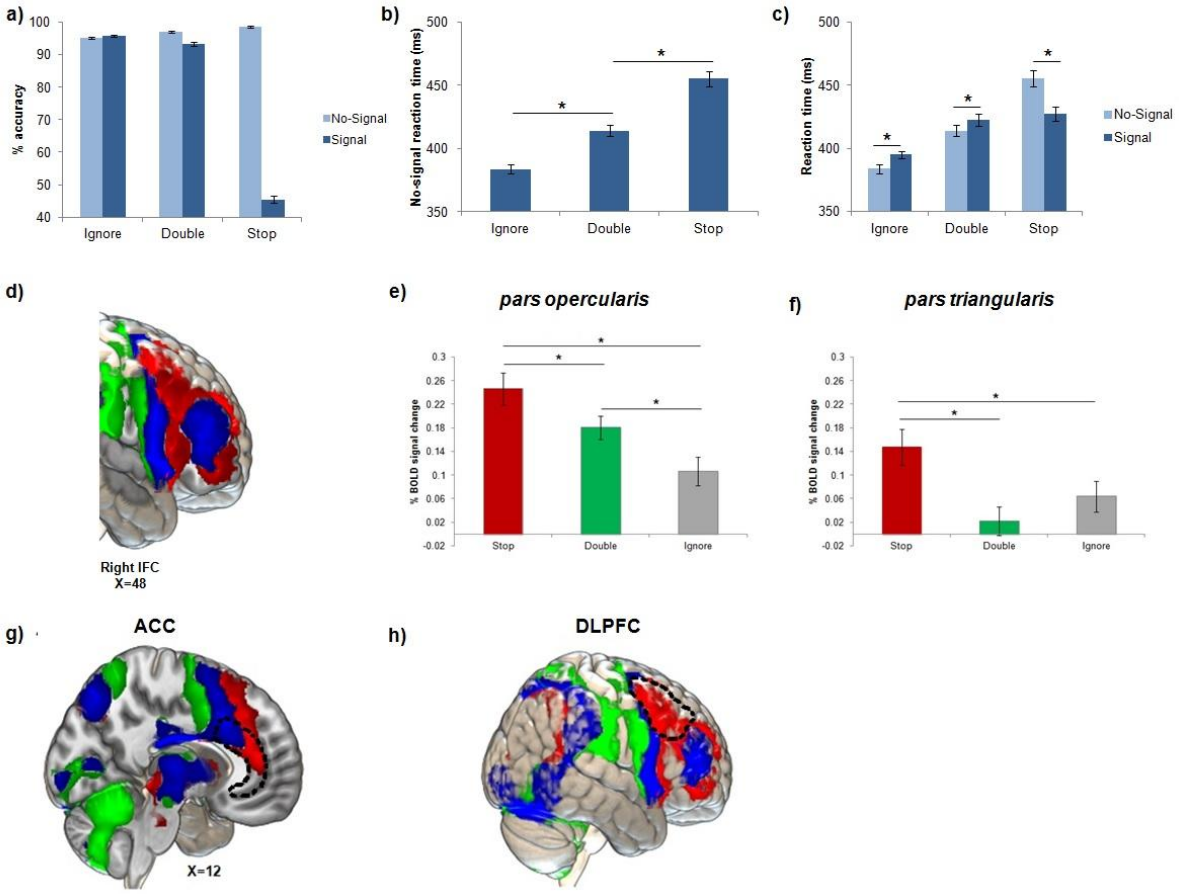


Figure 6.1. Overview of relevant findings from Study 1 (note that findings were very similar for Study 2). **(a)** % accuracy rates across signal and no-signal trials within each context; **(b)** demonstrates the significant difference between no-signal trial RTs across task contexts; **(c)** demonstrates the significant difference between signal and no-signal RTs within contexts. Note that in the DT, RTs to signal trials correspond to the execution of the first response, and in the SST, RTs to signal trials refer to failed stops. Remaining panels illustrate recruitment associated with the signal>no-signal contrasts for each task: SST=red, DT=green, overlap between SST and DT=blue, IT=grey. **(d)** illustrates the recruitment of the rIFG under different action updating conditions; **(e)** the difference in %BOLD change within the *pars opercularis*; **(f)** the difference in %BOLD change within the *pars triangularis*; **(g)** recruitment in the vicinity of the ACC (the area within the dashed black border) under different action updating conditions; **(h)** recruitment in the vicinity of the DLPFC (the area within the dashed black border) under different action updating conditions. *****=significant difference according to Holm-Bonferroni adjusted α. Error bars= ±1 within subject standard error (Cousineau, 2005; with correction, Morey, 2008).

The DLPFC and ACC are activated during (and predictive of) executive function (Blakemore & Choudhury, 2006; Fornito, Yücel, Wood *et al.*, 2004; Hara, Rapp, & Morrison, 2011) and are argued to be crucial for successful SST performance (e.g. Erika-Florence *et al.*, 2014; Chikazoe *et al.* 2009; Hughes *et al.*, 2013; Menon *et al.*, 2001; Sharp *et al.* 2010; Swick *et al.*, 2011; Swick & Jovanovic, 2002). In cognitive

control, the ACC and DLPFC have been hypothesised to be important for conflict monitoring (Botvinick *et al.,* 2001; Badre & Wagner, 2004; Kim, Chung, & Kim, 2010), performance monitoring and error detection (Brown & Braver, 2005; MacDonald, Cohen, Stenger & Carter, 2000; Sharp *et al.,* 2010) and working memory (Barber *et al.,* 2013). Although these processes are required for successful completion of all tasks in the context-cueing paradigm, enhanced ACC and DLPFC activity associated with the SST may signify the greater cognitive demands of this task. Furthermore, the DLPFC has been found to be recruited when response selection is required within stringent time–frames (Mars *et al.,* 2007). Moreover, the ACC is found to be active subsequent to inhibition failure and could be the source of error-related negativity in studies using electroencephalography (e.g. Dimoska *et al.,* 2006; Jodo & Kayama, 1992; Menon *et al.,* 2001; Senderecka *et al.,* 2012; see also Veen & Carter, 2002, Ridderinkhof *et al.,* 2004 and Yeung *et al.,* 2004 for reviews).

Additionally, in a typical SST, emphasis is placed on both the speed of responding (to ensure a prepotent response tendency is developed) and accuracy of signal detection (to ensure successful inhibition; Logan & Cowan, 1984; Verbruggen & Logan, 2009c). Proactive slowing of responses is commonly observed under SST conditions, and argued to be adopted to confer greater stop signal success (Verbruggen & Logan, 2009c). Such strategic adjustments may be induced by these conflicting task demands (Zhang, Hu, Chao *et al.*, 2012). Slowing of the initial response on DT signal trials relative to DT no-signal trials, and IT signal RTs relative to IT no-signal RTs were also observed (Figure 6.1a). It is possible that this is reflective of a partial 'braking' of responses induced by salient stimuli (Wessel & Aron, 2013; Aron *et al.,* 2014a); howevever, recent work has shown that the presentation of salient stimuli is more likely to recruit attentional mechanisms involved in stimulus detection as opposed to response inhibition (Leiva *et al.,* 2015). Therefore proactive response strategies may be adopted as a means to bias attention and neuronal processing towards particular stimulus features (Elchlepp *et al.,* 2015; Erika-Florence *et al.,* 2014a; Hampshire & Sharp, 2015a).

6.2.2. Overview of evidence from the literature

The pattern of rIFG activity under SST conditions supports the possibility that a reactive inhibitory module is housed within the rIFG (e.g. Aron *et al.*, 2003; Aron *et al.*, 2014a, 2014b, 2015; Aron, 2011). However, recent publications employing paradigms similar to the context-cueing paradigm find no evidence of rIFG-specialised inhibitory function (Chatham *et al.*, 2012; Dodds et al., 2011; Erika-Florence *et al.*, 2014; Hampshire *et al.* 2010; Hampshire, 2015; Tabu *et al.*, 2011; Verbruggen *et al.* 2010). Modular interpretations of frontal lobe function have been criticised for their over-simplification of the implementation of cognitive control. Importantly, functional specificity of the rIFG has been refuted in favour of network-wide mechanisms that support multiple processes that may not necessarily be inhibitory (see Hampshire & Sharp, 2015a, for a recent review). Hampshire *et al.* (Erika-Florence *et al.*, 2014; Hampshire, 2015; Hampshire & Sharp, 2015a, 2015b) argue that the patterns of activity observed in response inhibition studies are due to recruitment of the Multiple Demand Cortex (MDC; Duncan, 2000, 2001). They argue that this network is able to dynamically and rapidly adapt to various situations (see also Hampshire, Highfield, Parkin, & Owen, 2012). While the inclusion of the rIFG in the MDC is debatable (see Aron *et al.*, 2015), the discrepancies in the recruitment observed between my own work and that of others (Chatham *et al.*, 2012; Dodds et al., 2011; Erika-Florence *et al.*, 2014; Hampshire, 2015; Hampshire *et al.*, 2010; Tabu *et al.* 2011) may be the result of differential reliance on such networks under slightly different task conditions.

Alternatively, it could be argued that the anterior spread of rIFG activity observed in Studies 1 and 2 is associated with the proposed hierarchical organisation of the frontal lobes along the caudal-rostral axis (see Badre & D'Esposito, 2009, Botvinick, 2008, and Duncan, 2013 for reviews). It has been found that activity in more anterior regions of the lateral prefrontal cortex increases as either the information required to generate actions increases, or the complexity of the response required increases (e.g. Koechlin & Jubault, 2006; Koechlin, Ody, & Kouneiher, 2003; Badre & D'Esposito, 2009; Koechlin & Summerfield, 2007). Even though the instructions in the context-cueing paradigm are concrete as opposed to abstract (i.e. see signal in X context, perform Y action), the conflict between speeded responding and monitoring for stop signals as noted by Zhang *et al.* (2012) may increase the uncertainty in selecting the appropriate response. Indeed Badre and D'Esposito (2009) suggest that dissociation

between the anterior and mid ventrolateral prefrontal cortex depends on the ambiguity of the memory to be recovered (see also Levy & Wagner, 2011).

While the possibility that mental effort alone can account for increased activity along the rostro-caudal axis has been refuted (e.g. Koechlin *et al.* 2003), Hughes *et al.* (2013) have demonstrated otherwise. Under the independent horse race model (Logan & Cowan, 1984) it is assumed that if SSRT is greater than the time available for stopping (TAS), then responding to stop signals is likely. Hughes *et al.* (2013), posit that the shorter the TAS (with respect to SSRT), the more difficult the task. Increased rIFG activity was observed in response to 'hard' vs. 'easy' TAS conditions and was consistent even when the probability of inhibition was controlled for (see Figure 6.2). It should be highlighted that increases in task difficulty were met with anterior spread of activity within the rIFG similar to that associated with the SST in Studies 1 and 2 (see Figure 6.2. and Figure 6.1d). It is likely that the more 'difficult' task was associated with greater response conflict than the 'easy' condition and thus may be related to the uncertainty of responding as mentioned above (Badre & D'Esposito, 2009; Levy & Waganer, 2011; Zhang *et al.*, 2012).

Figure 6.2. Regions of activity observed when 'hard' vs. 'easy' stop-signal tasks were contrasted within participants when probability of inhibition was controlled for by Hughes *et al.* (2013).

Finally, the characteristic pattern of activity often found under conditions of response inhibition has been suggested to be the result of task complexities as opposed to the result of inhibition *per se*. Recent meta-analyses of go/no-go tasks (Criaud & Boulinguez, 2013; Simmonds *et al.*, 2008; Swick *et al.*, 2011) suggest that activations previously implicated in response inhibition could be accounted for by measures of task difficulty (e.g. number of stimuli, frequency of signals and working memory load).

Common networks of activity are often observed in studies employing both SST and go/no-go tasks (e.g. Rubia *et al.* 2001; Dambacher et al., 2014; Zheng, Oka, Bokura, & Yamaguchi, 2008; but see Eagle *et al.*, 2008; Schachar, Logna, Robaey *et al*., 2007). However, learning occurs more readily under go/no-go conditions and we cannot assume that the same inhibitory processes are recruited (Verbruggen & Logan, 2008). Thus whether these findings extend to account for activity associated with the SST is unclear. Nevertheless, greater right-lateralised activity found under SST, compared with go/no-go, conditions has been argued to be due to increased response selection demands (Rubia *et al.* 2001; see also Dodds *et al.*, 2011).

Together, these findings indicate the potential role the rIFG may play in responding to non-inhibitory task demands. As such, the disparity in rIFG activity associated with performance of the SST, compared with the DT and the IT, might not be indicative of a unique inhibition module as suggested by Studies 1 and 2 and further investigation is warranted.

6.3. The current work

To reiterate, the aim of the current work was to establish whether there are differences in the control demands required by the sub-tasks of the context-cueing paradigm. In Section 6.3.1, I outline analyses of cardio-respiratory measures acquired during Studies 1 and 2 (Study 1 = that which explored the neural correlates of inhibitory and non-inhibitory action updating using fMRI; Study 2 = that which explored the neurophysiology and neurochemistry of action updating using TMS/fMRI and MRS) . In Section 6.3.2, I present the findings from a study that employs the same behavioural task as outlined in Study 1, but includes additional measures of pupillometry and subjective ratings of perceived task-related difficulty and frustration.

6.3.1. Cardio-respiratory Analysis

In Studies 1 and 2, physiological noise correction was carried out to limit the confounding influence of physiological responses in brain activity (Bright & Murphy, 2013). Although removed from the fMRI analyses, cardio-respiratory measures may provide indices of the cognitive demands associated with the context-cueing paradigm.

Both cardiac and respiratory rates are found to be increased during periods of mental effort, time restrictions, increased working memory load and multi-tasking (e.g. Backs *et al.* 1991; Backs & Seljos, 1994; Carroll, Turner & Hellawell, 1986; Chen, Tsai, Biltz *et al.*, 2015; Fairclough & Houston, 2004; Fairclough, Venables, & Tattersall, 2005; Wientjes, 1992) and although naturally coupled (Yasuma & Hayano, 2004; Hirsch & Bishop, 1981), differences in the sensitivities of each measure to task demands (e.g. memory load, task difficulty and time restrictions) are also apparent (e.g. Veltman & Gaillard, 1998; Backs & Seljos, 1994). Cardio-respiratory recruitment has been proposed to support decision making (e.g. Jennings, Van Der Molen, & Debski, 2002), mediated by autonomic nervous system activity and implemented by the frontal lobes and ACC (Jennings *et al.*, 2002; Leech & Sharp, 2014; Van Boxtel, van der Molen, & Jennings, 2005; Matthews *et al.*, 2004; Zhang *et al.*, 2012). Thus, greater insights into autonomic nervous system modulation under different task demands may be granted by the inclusion of both cardiac and respiratory data.

If the anterior spread of activity in the rIFG associated with the SST in Studies 1 and 2 is presumed to be due to increased task demands (relative to the DT and IT), then cardiac and respiratory responses may be heightened relative to the DT or IT. On the other hand, if the SST is the least demanding of the tasks, then cardio-respiratory rates will be reduced for the SST relative to the DT or IT. Furthermore, I aimed to explore whether cardio-respiratory rates were related to the latencies of the inhibitory and non-inhibitory action updating processes (SSRT and DRT2) as well as when signals were presented. In the SST, signals presented prior to the 50%SSD are likely to be easier (as the probability of successful inhibition is high) relative to when signals are presented after the 50%SSD (as the probability of successful inhibition is low). Conversely, in the DT, the presence of the central decision bottleneck should render it more difficult to update responses at short SOAs relative to long SOAs (Telford, 1931; Welford, 1952).

6.3.1.1. Data Analysis

Separate analyses were conducted for the physiological measures of cardiac and respiration rates for subjects whilst they completed the context-cueing paradigm for Studies 1 and 2 (see Sections 2.2.1 and 4.3.2 for participants' demographic information).

Custom-written Matlab (Mathworks) scripts, SPSS (version 20; Armork, NY: IBM Corp.) and JASP (Version 0.7.5.6, Windows XP; JASP team, 2016)[92] were used to analyse the frequency of cardiac and respiratory measures separately for each study. The data acquired for each fMRI run during testing was divided into blocks- where the start of each block corresponded to the onset of the first fixation cross and the end of each block corresponded to the offset of the last stimulus. The number of peaks in the cardiac and respiratory traces enabled the measurement of heart and breathing rates. Precise measurement of cardio-respiratory frequency during task performance was ensured by discounting the cue time; thus preventing contamination of data by prolonged periods of preparation. Data were converted into beats and breaths per minute, means calculated for each block and divided according to task context. Note, that data corresponding to all trials were included in the analyses. Cardio-respiratory data were not examined on a trial-by-trial basis due to potential confounds of measurement acquired during neighbouring trials (i.e. data recorded within a trial may correspond to the previous trial). This is highly likely given normal adult healthy heart rate is approximately 60-100 beats per minute (Valentini & Parati, 2009), and respiration rate approximately 18 breaths per minute (Blows, 2001).

Cardiac and respiration rates were also correlated with behavioural indices of action updating as acquired for Studies 1 and 2. Repeated measures analyses of variance (ANOVA) and Pearson's correlations were conducted. Bayesian equivalents were computed for all Frequentist tests (Rouder et al., 2012; Rouder *et al., 2*009; Wetzels & Wagenmakers, 2012). Data screening was as presented in Section 2.3.3. The results presented here include parametric tests with no outlier exclusion. Results with outlier exclusion and non-parametric tests, where applicable, are reported in APP10.5.1. Inconsistencies between results are discussed.

6.3.1.2. Results

Repeated measures ANOVA for data acquired in Study 1 revealed differences in respiration rates between contexts ($F_{(2,58)}$=10.52, p<.001, BF=183.08; Figure 6.3a), where rates were found to be greater during DT performance relative to IT performance ($p_{.0167}$<.001, BF=677.31). However, although respiration rate was greater in the SST

[92] For Bayesian correlation analyses, custom written R code were used (supplied by R. Morey at Cardiff University) to set a JZS prior (as opposed to the Jeffrey's prior offered by JASP).

relative to the IT ($p_{.025}$=.026, BF=2.05), and the DT relative to the SST (p=.046, BF=1.28), the resultant BFs proved inconclusive. Analysis of respiration rates for Study 2 revealed no difference between the SST and DT ($t_{(29)}$=1.57, p=.129, BF=0.58). However, respiration rate for the DT was found to be reliably greater than the SST after outlier removal ($t_{(28)}$=2.54, p=.017, BF=2.93; APP10.5.1.1), suggesting increased demands associated with the DT over the SST.

Cardiac rates were also found to differ across the contexts in Study 1 ($F_{(2,58)}$=5.13,$p_{.05}$=.009, BF=8.63) and were reliably higher in the DT relative to the SST ($p_{.0167}$=.005, BF=8.63). The differences between cardiac rate in the DT and IT (p=.09, BF=0.76) and the SST and the IT (p=.142, BF=0.54) proved inconclusive. The difference in cardiac rates between contexts was not replicated after analysis of the data acquired in Study 2 ($t_{(29)}$=1.45, p=.157, BF=0.5).

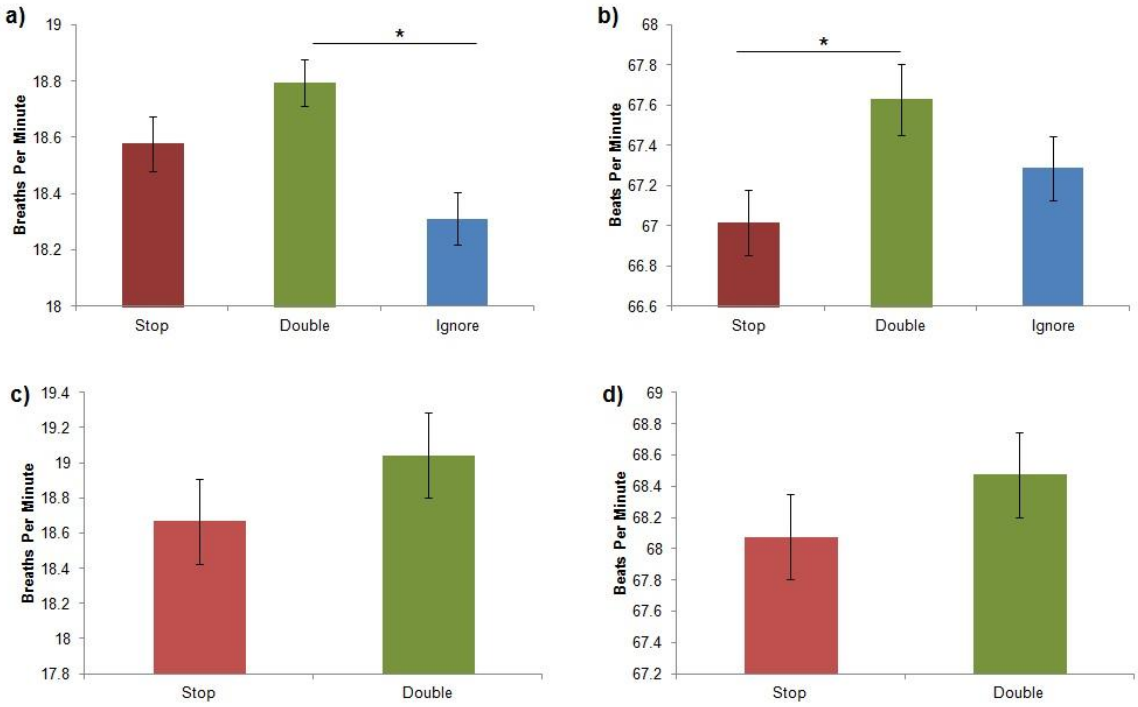


Figure 6.3. Differences in cardiac and respiration rates across the tasks comprising the context-cueing paradigm. **(a)** Represents differences in respiration rate in Study 1, **(b)** represents differences in cardiac rate in Study 1, **(c)** represents differences in respiration rate in Study 2, **(d)** represents differences in cardiac rate in Study 2. Note that subsequent to outlier exclusion, significant differences in respiration rates were found between contexts in Study 2 (APP10.5.1.1). *****=significant difference according to Holm-Bonferroni adjusted α. Error bars= ±1 within subject standard error (Cousineau, 2005; with correction, Morey, 2008).

Mean cardiac and respiration measures for both studies were consistent with previous reports in healthy participants (Valentini & Parati, 2009; Blows, 2001; see Table 6.1 and also Figure 6.3). No correlations were found between cardiac and respiratory rate in the SST (Study 1: $r_{(28)}$=0.07, *p*=.706, BF=0.21; Study 2: $r_{(28)}$=0.3, *p*=.106, BF=0.66), DT (Study 1: $r_{(28)}$=0.13, *p*=.503,BF=0.24; Study 2: $r_{(28)}$=0.31, *p*=.099, BF=0.72) or in the IT (Study 1: $r_{(28)}$=0.14, *p*=.474, BF=0.25). Although note that subsequent to outlier exclusion, a positive relationship was identified between cardiac and respiration rates in the DT ($r_{(28)}$=0.44, *p*=.020, BF=3.22). Behavioural indices of action updating efficiency were found not to be related to either cardiac or respiration rate in either the SST or DRT2 (Table 6.2).

Table 6.1. Mean and standard deviations of respiration and cardiac rates in the context-cueing paradigm for Studies 1 and 2.

Measure	Study	SST	DT	IT
Respiration Rate	1	18.58	18.79	18.31
(brpm)		*2.41*	*2.44*	*2.47*
	2	18.07	19.04	N/A
		3.89	*4.24*	N/A
Cardiac Rate	1	67.01	67.63	67.29
(bpm)		10.29	10.56	10.16
	2	68.08	68.47	N/A
		9.73	*9.35*	N/A

Note. Standard deviations for each measure are reported below the corresponding means in italics. Respiration rate is reported in breaths per minute (**brpm**) and cardiac rate is reported in beats per minute (**bpm**). The IT was not employed in Study 2 and thus corresponding rates are not reported (**N/A**).

Table 6.2. Summary of correlations conducted between cardiac rate and behavioural indices of action updating and between respiration rate and behavioural indices of action updating in Studies 1 and 2.

Study	DVs		r	*p*	BF
Study 1	Mean SSRT	SST Cardiac	0.28	.14	0.56
		SST Resp	-0.12	.515	0.24
	Integ SSRT	SST Cardiac	0.17	.371	0.28
		SST Resp	-0.16	.408	0.27
	p(respond|signal)	SST Cardiac	-0.17	.37	0.28
		SST Resp	-0.05	.789	0.2
	DRT2	DT Card	-0.12	.523	0.23
		DT Resp	-0.05	.794	0.2
	Bottleneck	DT Card	-0.29	.121	0.61
		DT Resp	0.04	.816	0.2
Study 2	Integ SSRT	SST Cardiac	-0.03	.92	0.2
		SST Resp	0.16	.434	0.27
	p(respond|signal)$^{+}$	SST Cardiac	<0.01	.979	0.19
		SST Resp	0.12	.518	0.23
	DRT2	DT Card	0.27	.153	0.52
		DT Resp	0.15	.407	0.19
	Bottleneck	DT Card	-0.33	.071	0.87
		DT Resp	-0.13	.499	0.24

Note. **DVs**=dependent variables; **r**=Pearson's correlation coefficient; ***p***=p-value; **BF**= Bayes Factor; **Mean SSRT**= SSRT as estimated using the mean method; **Integ SSRT**= SSRT as estimated using the integration method; **p(respond|signal)**= the probability of responding to a stop signal trial; **DRT2**=the latency of the double-response process; **Bottleneck**= size of the bottleneck on double-signal trials as quantified in Section 2.3.1. $^{+}$=non-parametric tests required. All degrees of freedom=29.

6.3.1.3. Cardio-Respiratory Discussion

In general, the DT was found to be related to greater cardio-respiratory rates than in the SST and IT, and thus appears to be the most demanding. This finding was unexpected given the increased error-likelihood and response conflict associated with signal presentation in the SST relative to the DT. However, the significant differences between measures acquired for each task were inconsistent across Studies 1 and 2. While cardiac rates were significantly higher in the DT relative to the SST in Study 1, this was not replicated in Study 2. Conversely, respiration rates between the SST and DT were not reliably different in Study 1, but the DT was associated with greater respiratory rates, relative to the SST, in Study 2 (subsequent to outlier exclusion). These inconsistencies are likely associated with variability in these measures. Thus, although the general pattern of results indicates that the DT is more demanding than the SST, a larger sample size is required to enhance the stability of such inferences. The insensitivity of cardio-respiratory rates to detect subtle differences in cognitive effort might also explain the

lack of correlational relationships between cardio-respiratory rates and behavioural indices of action updating (Table 6.2).

Furthermore, it is also possible that the pattern of results observed here could be the consequence of increased physical, as opposed to mental, effort. Indeed, cardiac rates have been found to be elevated in even the simplest of motor tasks, including grip responses (Jennings, van der Molen, Somsen & Terezis, 1990). Thus the increase in cardiac and respiratory rates associated with the DT could be the result of the requirement to execute an additional response on double signal trials. The increased physical, as opposed to mental, exertion could also explain the lack of difference between cardio-respiratory rates acquired under SST, relative to IT, conditions.

The lack of difference between cardio-respiratory measures between the SST and IT was unexpected. It was anticipated that the SST was the more mentally efforful than the IT, given the requirement to update (inhibit) an on-going action plan on signal trials in the SST and not in the IT. Speculatively, it is possible that the absence of differences in cardio-respiratory rates between these tasks (and the difference between DT and SST) may be due to autonomic slowing in the SST. Heart rate deceleration occurs prior to response execution in all tasks (Coles & Duncan-Johnson, 1975) and this is often interpreted as the result of response selection (Jennings *et al.,* 1992) and preparation (Coles & Duncan-Johnson, 1975; Jennings *et al., 2*002) demands. Response preparation demands are likely greater in the SST, relative to the DT and IT (evidenced by proactive slowing). As such, cardiac rates in the SST may be reduced overall in spite of increased cognitive demands. Cardiac rates are also likely to be reduced in response to errors and negative feedback (Van Der Veen, Nieuwenhuis, Crone, & Van der Molen, 2003), for which the likelihood is larger in the SST relative to the DT and IT. Consistent with this, cardiac rates have been found to decrease on unsuccessful signal trials in both SST and go/no-go tasks (Van Boxtel & van der Molen, 2001; Jennings, van der Molen, Brock, & Somsen, 1992; Van Boxtel, van der Molen & Jennings, 2005).

In summary, there was no substantial evidence to indicate the SST to be more cognitively demanding or effortful than the DT. Thus, it is possible that the pattern of activity in the anterior rIFG is illustrative of a specialised inhibitory module. However, the nature of the pattern of results requires clarification, given the potential for physical and autonomic differences between tasks. Exploration of trial-by-trial variability in

physiological measurement would likely assist in the interpretation of these findings. This is explored in the next section.

6.3.2. Study 3: Pupillometry and self-Report

Like cardio-respiratory measures, pupillary responses are controlled by the autonomic nervous system and have been used as indices of mental effort (see Beatty, 1982 and Sirois & Brisson, 2014, for reviews). Previous work has shown linear increases in pupil dilation associated with increased working memory load and task complexity and also in dual-task settings (e.g. Beatty & Kahneman, 1966; Kahneman, Beatty & Pollack, 1967; Piquado, Isaacowitz & Wingfield, 2010) and have been proposed to reflect decision thresholds (Cavanagh, Wiecki, Kochar, & Frank, 2014). I therefore assessed whether such differences could be established within and between the sub-tasks comprising the context-cueing paradigm.

Pupil diameter is typically found to be increased subsequent to an error relative to a correct response (Critchley, Tang, Glaser *et al.*, 2005; Wessel, Danielmeier, & Ullsperger, 2016) and as such would be expected to be elevated on signal trials in the SST, relative to DT or IT due to the greater number of associated errors. However, opposing findings have been reported in previous work. Specifically, Chatham *et al.* (2012) found increased pupil diameter during no-signal trials in both SST and DT relative to stop-signal trials. In addition, increased pupil diameter on no-signal trials in the SST relative to no-signal trials in the DT was taken as evidence of increased error monitoring when a change in response was possible. Finally, pupil diameter was found to be increased on signal trials presented in the DT relative to those in the SST - for which Chatham *et al.* (2012) argues demonstrates increased effort in response execution compared with response inhibition.

Given these discrepancies, it was unclear whether the SST or DT was expected to be associated with increased pupil diameter. Furthermore, as identified above, there was potential for confounds associated with physical exertion and autonomic slowing which could have impacted on the interpretability of results. Thus, as the IT requires no action updating, its inclusion was anticipated to help untangle these effects (as per the cardio-respiratory analyses above). Self-report measures of task-related difficulty and frustration were also incorporated to obtain subjective measures of cognitive effort. The

inclusion of self-report measures was expected to confer greater sensitivity than the objective measures used thus far (Garofalo & Lester, 1985; Gift, 1989; Jahedi & Méndez, 2014; although correlations between psycho-physiological and self-report measures of mental effort are closely related across a variety of tasks; e.g. Carroll, Douglas, Turner, Rick & Hellawell, 1986; Siegle, Steinhauer, Carter *et al.*, 2003; Zénon, Sidibé, & Olivier, 2014). This was deemed particularly important given the potential for psycho-physiological measures to vary with physical as well as mental exertion (e.g. Zénon *et al.*, 2014).

Previous work has explored the relationship between task-related frustration and %BOLD associated with inhibitory control (Li, *et al.*, 2006, 2008; Spunt, Lieberman, Cohen & Eisenberger, 2012). However, these investigations have yielded mixed results. Spunt *et al.* (2012) established increased ACC activity with increased task-related frustration in the SST, but no relationships were established by Li *et al.* (2006, 2008) when exploring BOLD changes in the superior and prefrontal cortices. It is likely that these discrepancies are the result of differences in the way in which self-report ratings were measured. The use of extreme descriptors at either end of a Likert scale by Li *et al.* (2006, 2008, "minimal" stress and "most frustrating and stressful ever") likely encouraged dichotomous responses, either towards or away from the extreme (Gift, 1989). More subtle descriptors employed by Spunt *et al.* (2012; "not at all" vs. "extremely") likely provided greater measurement sensitivity to detect effects. In the current study, I avoided the use of extreme descriptors and used Visual Analogue Scales (VAS[93]) to maximise the sensitivity of subjective ratings of task-related frustration and difficulty.

To evaluate the pattern of results in more detail, I also assessed behavioural indices of action updating in relation to both self report and pupillometry results. As above, I aimed to explore whether these measures were related to the latencies of the inhibitory and non-inhibitory action updating processes (SSRT and DRT2) as well as when signals were presented (i.e. pre vs. post 50%SSD and within- vs. post decision bottleneck). As in the previous section, if pupillometry and self-report data indicate the SST to be the more demanding of the tasks, rIFG activity yielded in Studies 1 and 2 could be interpreted as the result of control processes that are not inclusive of response inhibition *per se*.

[93] VAS have been advocated over Likert-type scales when precision and sensitivity of responses is required (Gift, 1989).

6.3.2.1. Materials and Methods

6.3.2.1.1. Participants

30 right-handed participants (23 females) aged between 18 and 29 years (*M*=22.83 years, *SD*=3.87) completed the study. All participants had normal or corrected-to-normal vision and normal colour vision. Participants were recruited from a University-wide advertisement and were reimbursed £21 for their time. The study received ethical approval from the Ethics Committee at the School of Psychology, Cardiff University.

6.3.2.1.2. Study design

Participants completed a separate training and testing sessions as per Studies 1 and 2. The context-cueing paradigm was presented exactly as in Study 1; however, key differences between the studies are noted below:

1. Participants completed both sessions in a laboratory environment as opposed to an MRI (or mock scanning) environment and so were seated rather than lying supine during the sessions.

2. Responses were recorded via the use of a standard keyboard rather than a lumitouch response box (keys ‘j’ and ‘k’ were used to indicate the direction of the arrow, and the ‘space’ key was used to execute the additional thumb response as required on signal trials in the DT).

3. In the testing sessions, participants completed 6 behavioural runs of the context-cueing paradigm as opposed to 8 as in Study 1 due to logistical constraints.

4. Participants positioned their head in a chin rest throughout the testing session to ensure stable eye-tracking. An eye-calibration was carried out prior to each behavioural run to ensure accurate tracking (see Section 6.3.2.1.3).

5. Participants provided self-report ratings of perceived task-related difficulty and frustration on VAS after each task block (see Section 6.3.2.1.4.).

All instances of feedback and alteration of the theoretical 50%SSD (using psychophysical inhibition functions) were identical to those procedures outlined in Study 1 (Section 2.2.3).

6.3.2.1.3. Eye-tracking

An infrared 250Hz Cambridge Research Systems monocular Eye-tracker (Cambridge Research System Ltd) was used in conjunction with VideoEyetrace (version 3.20, toolbox version 3.221; Cambridge Research System Ltd). Participants were positioned in a chin rest to minimise head movement and to ensure stability in tracking throughout. Pupil diameter was recorded from the onset to the offset of each stimulus for each trial.

6.3.2.1.4. Visual analogue scales

Two VAS, each with a length of 500 pixels[94], were presented at the end of each task block. Anchors were presented at either end of the scales, equidistant from the centre. The descriptors "not at all" and "very" were positioned beneath each anchor and were designed to capture participants' perceived difficulty and frustration to each of the tasks. The question "how difficult did you find the task?" or "how frustrating did you find the task?" was presented above each scale (Figure 6.4). Participants were instructed to respond to the questions according to the task completed in the previous block. The order of questions and whether each descriptor was positioned beneath the left or right anchor was randomised across blocks.

[94] Scale length of 500 pixels has been recommended for computer-based research with screen resolution 1024x768 as used here (Marsh-Richard, Hatzis, Mathias *et al.*, 2009). Although shorter lengths have been recommended elsewhere (e.g. 200 pixels suggested by Reips & Funke, 2008), evidence suggests that VAS are interpreted in the same way regardless of length, with participants performing similarly when required to identify different values (e.g. percentages, ratios) along scales varied in length between 200 and 800 pixels (Reips & Funke, 2008).

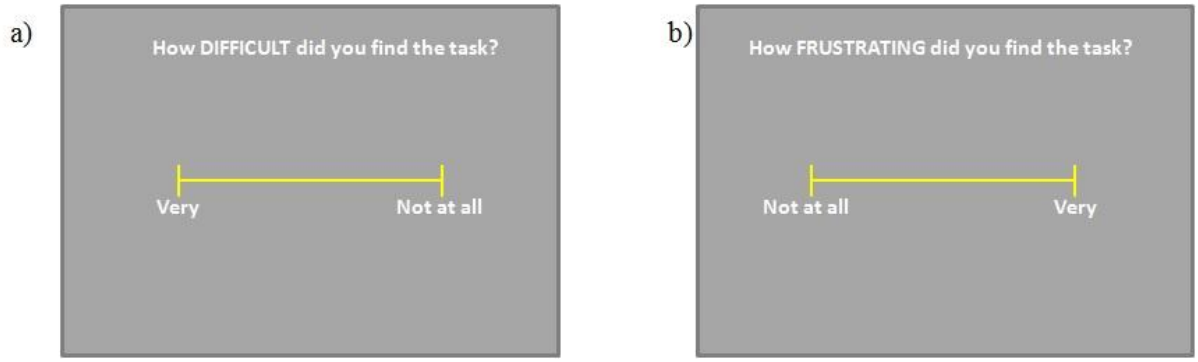


Figure 6.4. Illustration of the visual analogue scales used to measure task-related **(a)** 'difficulty' and **(b)** 'frustration'. The scales and whether descriptors were presented beneath the left of right anchors, was randomised within participants.

To reflect their response to each scale, participants were required to position a cursor onto a relevant point and to press any key on a standard keyboard. The additional key press prevented the execution of erroneous responses made by unintentional mouse clicks. Mouse movement was limited to prevent positioning of the cursor beyond the extremes of the scales. Once a response was recorded, participants were presented with the words "please wait" on the screen for 2,000ms and then the alternative (difficulty or frustration) VAS was presented. The mouse cursor was re-positioned to the centre of the screen with the onset of each scale to prevent any initial bias towards either end of the scales.

6.3.2.2. Data analysis

Behavioural dependent measures analysed here included measures of the latency of the inhibitory and non-inhibitory action updating (SSRT and DRT2) computed as per Study 1 (Section 2.3.1). Note that only the integration method (Logan & Cowan, 1984) was used to estimate SSRT. The quantification procedure outlined in Section 2.3.1 was used to estimate the size of the PRP (Section 2.3.1) and to divide signal trials in the DT according to whether they were presented within the decision bottleneck period or in the post-bottleneck phase (computed separately for each participant). This was used to establish whether differences in pupil diameter differed between these two decision phases. Data were also divided according to whether stop signals were presented prior

to or after the 50%SSD. Additional dependent measures included proactive slowing[95] and p(respond|signal) in the SST.Self-report ratings were computed based on the X-axis position of the cursor (in pixels) with reference to the position of the "not at all" anchor for both scales. The larger the rating value, the more difficult or frustrating the task was deemed. Ratings were converted from pixels to % to ease interpretation.

Mean pupil diameter was calculated for each trial from the onset to the end of each arrow stimulus. Instances of 0mm pupil diameter (indicating blinking or interrupted eye-tracking) were excluded from the analysis. Data were analysed using custom-written Matlab scripts, SPSS (version 20; Armork, NY: IBM Corp.) and JASP (Version 0.7.5.6, Windows XP; JASP Team, 2016)[96]. Data were divided according to corresponding task contexts and trial-types and entered into repeated measures ANOVA to establish whether task-related variations in pupil diameter were present. Separate ANOVAs were conducted for signal and no-signal trials. Paired sample t-tests were conducted to establish the presence of within-task differences between signal and no-signal trials. Correlation analyses were used to explore the relationships between measures. Bayesian equivalents were computed for all Frequentist tests (Rouder *et al., 2*009, 2012; Wetzels & Wagenmakers, 2012). Data screening was as presented in Section 2.3.3. The results presented here include parametric tests with no outlier exclusion. Results with outlier exclusion and non-parametric tests, where applicable, are reported in APP10.5.1.2. Inconsistencies between results are discussed.

6.3.2.3. Results

Behavioural results were as found in Studies 1 and 2. All accuracy and RT data were within the pre-specified performance benchmarks (Section 2.2.3 and Figure 6.5a-c). RTs to no-signal trials were found to reliably differ across the contexts ($F_{(1.36,39.34)}$=65.63, $p_{.05}$<.001, Greenhouse-Geisser corrected, BF=4.19^{e+12}), with those in the SST longer than those in the DT and IT, and those in the DT longer than the IT (all p<.001, BF>179.7). The RT of the initial response on DT signal trials was longer than the RT to no-signal trials in the DT ($t_{(29)}$=2.28, $p_{.05}$=.024, BF=2.17). Signal RTs were

[95] Computed as the difference in mean RTs to no-signal trials in the SST and IT for each participant.
[96] For Bayesian correlation analyses, the Matlab scripts supplied by Sam Schwarzkopf (http://sampendu.wordpress.com/bayes-factors/) were used to set a JZS prior (as opposed to the Jeffrey's prior offered by JASP).

also longer than no-signal RTs in the IT ($t_{(29)}$=4.35, $p_{.025}$<.001, BF=175.77). Conversely, RTs for failed stops on stop signal trials were shorter than RTs to no-signal trials in the SST ($t_{(29)}$=8.99, $p_{.0167}$<0.001, BF=1.59$^{e+7;}$ see Figure 6.5b).

Stop signals were successfully inhibited 45.09% (*SD*=6.12%) of the time, corroborating the use of psychophysical inhibition functions to set the SSDs during the testing session. The average estimated SSRT was 221.87m s (*SD*=39.38ms). Reliable PRPs were found for each participant (adjusted R^2=89.01%, *SD*=4.38). DRT2 was longer at the shortest SOA ($F_{(1.17,33.86)}$=116.68, $p_{.05}$<.001, Greenhouse-Geisser corrected, BF=2.66^{e+19}) than that at the intercept and final SOA, with an increase in DRT2 between the intercept and final SOA (all *p*<.001, all BF>1.9^{e+15}**).**

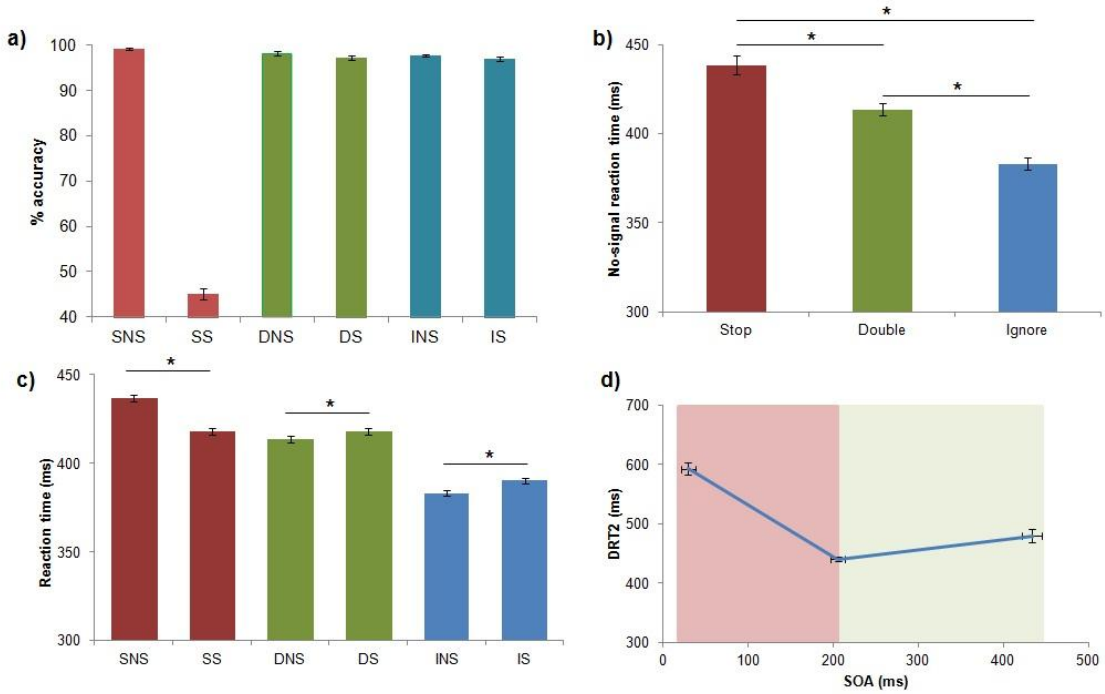


Figure 6.5. Behavioural results of Study 3. **(a)** % accuracy across trial types; **(b)** the difference in mean no-signal RTs across contexts; **(c)** the difference in mean RTs across between signal and no-signal trials across contexts. Note that in the SST, signal RTs refer to the RT of failed stops, and in the DT, signal RTs refer to the RT of the initial response on DT signal trials; **(d)** the mean PRP across participants. **SNS**= go trials in the SST; **SS**= signal trials in SST; **DNS**= go trials in the DT; **DS**= signal trials in the DT; **INS**= go trials in the IT; **IS**= signal trials in the IT. In panel **(d)**, the pink area represents the bottleneck phase and the green area represented the post-bottleneck phase., **SOA**= signal onset asynchrony, **DRT2**= reaction time of the additional response as required in the double-response task. *****=significant difference according to Holm-Bonferroni adjusted α. Error bars**=** ±1 within subject standard error (Cousineau, 2005; with correction, Morey, 2008).

Self-report ratings are summarised in Figure 6.6. Repeated measures ANOVA revealed differences in task-related difficulty and frustration between contexts ($F_{(1.63,47.12)}$=93.14, p<.001, Greenhouse-Geisser corrected, BF=1.91^{e+18} and $F_{(1.74,50.55)}$=110.2, $p_{.05}$<.001, Greenhouse-Geisser corrected, BF= 9.06^{e+18}, respectively). The SST was found to be the most difficult, and the IT the least difficult (all p<.001, BF>1446.27). The SST was also found to be more frustrating and the IT the least frustrating (all p<.009, all BF>5.03). Significant positive correlations were found between ratings of task-related difficulty and frustration within each context (SST: $r_{(28)}$=0.8, $p_{.0167}$<.001, BF=135632; DT: $r_{(28)}$=0.78, $p_{.05}$<.001, BF=44315.42; IT: $r_{(28)}$=0.79, $p_{.025}$<.001, BF=76337.11)[97]. While the SST was the most difficult and frustrating, corresponding ratings were on average at 49.57% and 55.53%, respectively (Figure 6.6). Thus it could be considered that the SST was not deemed particularly difficult or frustrating, but was more so than the DT and IT.

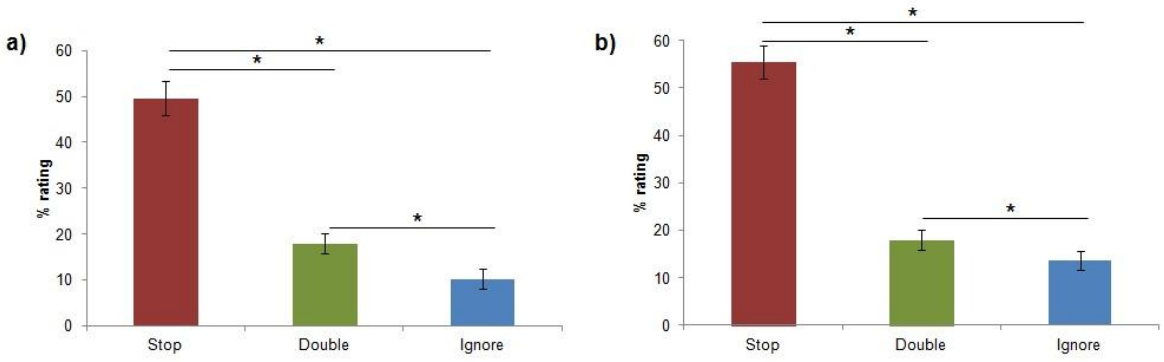


Figure 6.6. Differences in task-related **(a)** difficulty and **(b)** frustration across each of the task contexts. *****=significant difference according to Holm-Bonferroni adjusted α. Error bars= ±1 within subject standard error (Cousineau, 2005; with correction, Morey, 2008).

Self-report measures of task-related difficulty and frustration appeared to be independent of indices of action updating (Table 6.3). Evidence for relationships were in favour of the null and thus while more evidence is required it appears that the self-

[97] These strong positive correlations between participant ratings of task-related difficulty and frustration indicate that the two measures may not be independent and may be interpreted in the same way by participants. This would also provide reason for the highly similar findings yielded throughout these analyses, The rationale for considering both terms was to explore different 'descriptors' that participants may use to convey how 'demanding' they found the tasks.

report ratings may be general to the task-design as opposed to related to how participants specifically perform the tasks.

No differences in pupil diameter were found between tasks (see Figure 6.7). Repeated measures ANOVA revealed no difference in mean pupil diameter between contexts regardless of whether all trials ($F_{(1.22,35.38)}$=1.45, p=.243, Greenhouse-Geisser corrected, BF= 0.31), signal only trials ($F_{(1.23,35.65)}$=1.06, p=.35, Greenhouse-Geisser corrected, BF=0.84) or no-signal trials ($F_{(1.23,35.64)}$=2.78, p=.1, BF=0.23) were considered. Evidence for each of these ANOVAs favoured the null. Although the patterns of activity were in line with those reported by Chatham *et al.*(2012), no difference was found between pupil diameter on no-signal trials in the DT and SST relative to stop-signal trials ($t_{(29)}$=0.50, p=.618, BF=0.22 and $t_{(29)}$=0.81, p=.423, BF=0.26, respectively)[98]. Furthermore, within task contexts there was no difference between signal and no-signal trials in the SST ($t_{(29)}$=0.81, p=.423, BF=0.26) or in the IT ($t_{(29)}$=0.16, p=.88. BF=0.2). However, mean pupil diameter on signal trials in the DT was increased relative to no-signal trials ($t_{(29)}$=2.99, $p_{.0167}$=.006, BF=7.28). This finding suggests that the effort involved in detecting a signal and executing an additional response is greater than that of executing a single response only.

If the difference in mean pupil diameter between the signal and no-signal trials in the DT was due to mental effort, it would be anticipated that pupil diameter would also be greater when the execution of the additional response is also more difficult; i.e. when signals are presented within-, as opposed to post-, decision bottleneck (if assumed the bottleneck is not the result of strategic response adjustment). However, no difference in pupil diameter was found when double-signal trials were presented prior to the bottleneck relative to post-bottleneck ($t_{(29)}$=.57, p=.572. BF=0.23). Furthermore, no correlations between mean pupil diameter, DRT2 and the size of the decision bottleneck were found (Table 6.4). Therefore, it seems unlikely that mental effort alone can account for the difference in pupil diameter between signal and no-signal trials in the DT. Mental effort also appeared to be unrelated to pupil diameter in the SST, when explored in relation to behavioural indices of inhibitory action updating (Table 6.4).

[98] Subsequent to outlier removal, pupil diameter was found to be increased on signal relative to no-signal trials in the SST, but the evidence was in favour of the null (BF=0.2).

Table 6.3. Correlations between behavioural indices of action updating and self-report ratings of task-related difficulty and frustration.

DVs		r	*p*	BF
SSRT	SST Diff	-0.11	.551	0.23
	SST Frust	-0.06	.737	0.26
p(respond|signal)	SST Diff	0.31	.091	0.72
	SST Frust	0.33	.073	0.87
Proac Slow^{+}	SST Diff	-0.12	.530	0.23
	SST Frust	-0.1	.589	0.22
DRT2	DT Diff	-0.13	.501	0.24
	DT Frust	-0.13	.575	0.24
Bottleneck	DT Diff	-0.04	.850	0.2
	DT Frust	-0.13	.498	0.24

Note. **DVs**=dependent variables; **r=**Pearson's correlation coefficient; ***p***=*p*-value; **BF**-Bayes Factor; **SSRT**=stop signal reaction time as estimated using the integration method; **p(respond|signal)**=the probability of responding to stop signal trials; **Proac Slow=**proactive slowing, computed as the difference between the mean reaction time to no-signal trials in the IT subtracted from the mean reacyion time to no-signal trials in the SST; **DRT2**= the latency of the non-inhibitory updating process; **Bottleneck**= the size of the bottleneck as quantified using the procedure outlined in Section 2.3.1; **Diff**=task-related difficulty; **Frust**=task-related frustration; $^{+}$=computed based on square-root transformed data. All degrees of freedom=28.α-level for comparison not shown as all *p*>.05.

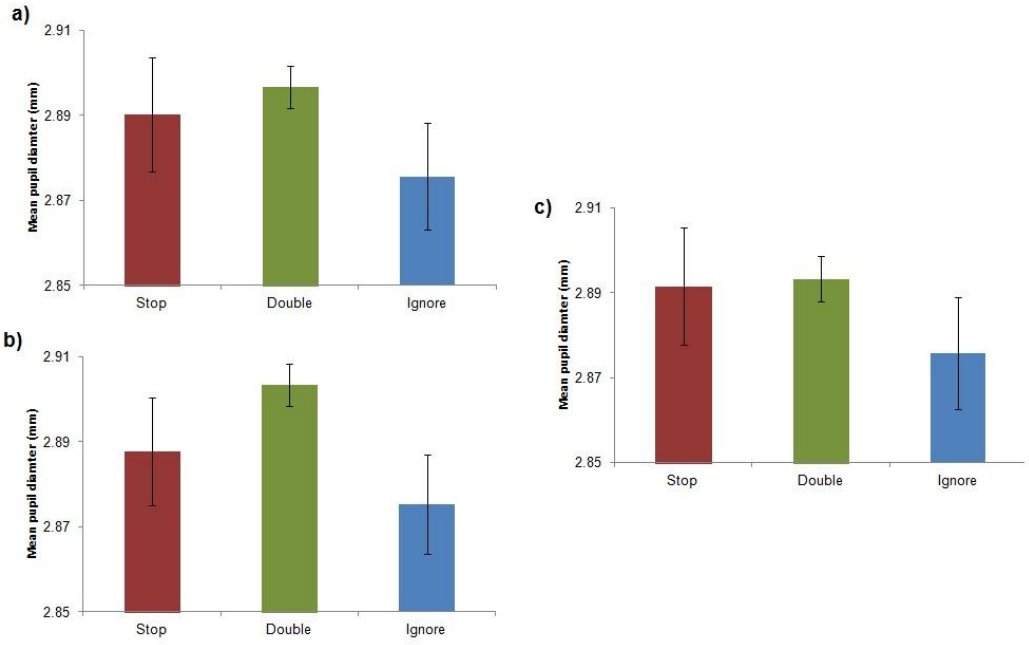


Figure 6.7. Mean pupil diameter across each task context for **(a)** all trials; **(b)** signal trials; and **(c)** no-signal trials. No significant differences in pupil diameter were found across contexts and all BFs were <1/3, indicating substantial favour of H_0.

Table 6.4. Correlations between behavioural indices of action updating and pupil diameter across the SST and DT.

DVs		r	*p*	BF
SSRT	S All	0.02	.912	0.2
	SS	0.04	.851	0.2
	SNS	0.01	.943	0.2
p(respond|signal)	S All	-0.09	.647	0.22
	SS	-0.09	.620	0.22
	SNS	-0.08	.662	0.21
Proac Slow^{+}	S All	0.02	.921	0.2
	SS	0.02	.914	0.2
	SNS	0.02	.924	0.2
DRT2	D All	0.1	.591	0.22
	DS	0.1	.589	0.22
	DNS	0.1	.591	0.22
Bottleneck	D All	0.24	.197	0.42
	DS	0.24	.197	0.42
	DNS	0.24	.197	0.42

Note. **DVs**=dependent variables; **r**=Pearson's correlation coefficient; ***p***=*p*-value; **BF**-Bayes Factor; **SSRT**=stop signal reaction time as estimated using the integration method; **p(respond|signal)**=the probability of responding to stop signal trials; **Proac Slow=**proactive slowing, computed as the difference between the mean reaction time to no-signal trials in the IT subtracted from the mean reaction time to no-signal trials in the SST; **DRT2**= the latency of the non-inhibitory updating process; **Bottleneck**= the size of the bottleneck as quantified via the procedure outlined in Section 2.3.1; **S=** SST; **D**=DT; **Diff**=task-related difficulty; **Frust**=task-related frustration; $^{+}$=computed based on square-root transformed data. All degrees of freedom=28. α-level for comparison not shown as all $p>.05$.

Finally, no relationships between mean pupil diameter and self-report ratings of task difficulty of frustration were found across any of the task contexts (Table 6.5). However, after outlier exclusion (APP10.5.4) BFs were found to be inconclusive. Interestingly pupil diameter appeared to generally constrict with increasing ratings of task-related difficulty and frustration in the SST, and task-related frustration in the DT-opposite to what would be expected if increased task-related frustration and task-related difficulty were due to increased task demands (i.e. a positive correlation was expected based on previous work; e.g. Beatty & Kahneman, 1966; Kahneman *et al.,* 1967; Piquado *et al.,* 2010). More evidence is required to substantiate if this is indeed an effect.

Table 6.5. Correlations between self-report measures of task-related difficulty and frustration with pupil diameter across the SST, DT and IT.

DVs		r	*p*	BF
SST Diff	S All	-0.15	.434	0.26
	SNS	-0.15	.436	0.26
	SS	-0.15	.430	0.26
SST Frust	S All	-0.13	.500	0.24
	SNS	-0.13	.504	0.24
	SS	-0.13	.493	0.24
DT Diff	D All	0.05	.813	0.2
	DNS	0.04	.816	0.2
	DS	0.05	.808	0.2
DT Frust	D All	-0.22	.239	0.37
	DNS	-0.22	.242	0.37
	DS	-0.22	.237	0.37
IT Diff^{+}	I All	-0.02	.934	0.2
	INS	-0.02	.937	0.2
	IS	-0.02	.930	0.2
IT Frust^{+}	I All	-0.05	.799	0.2
	INS	-0.05	.802	0.2
	IS	-0.05	.793	0.2

Note. **DVs**=dependent variables; **r**=Pearson's correlation coefficient; ***p***=*p*-value; **BF**-Bayes Factor; **Diff**=task-related difficulty; **Frust**=task-related frustration; **All**=mean pupil diameter across all trials within the corresponding context; **NS**= mean pupil diameter across no-signal trials within the corresponding context; **SS/DS/IS**= mean pupil diameter across signal trials in the SST, DT and IT, respectively; $^{+}$=computed based on square-root transformed data. All degrees of freedom=28. α-level for comparison not shown as all $p>.05$.

6.3.2.4. Study 3 discussion

Self-report data revealed significantly elevated ratings of subjective task-related difficulty and frustration associated with the SST, relative to the DT and IT. Given the evidence from the literature and from the Studies 1 and 2 regarding the possible demands associated with the SST, this is not unexpected. If the subjective reports are accurate, then the anterior spread of activity in the rIFG through the *pars opercularis* and *pars triangularis,* may well be influenced by differences in control demands associated with the SST relative to the DT and the IT. However, no differences were found between tasks when explored in relation to pupil diameter.

The pupillometry results alone suggest that responding to double-signal trials is more demanding than responding to no-signal trials in the same context only. A benefit of repeating the behavioural elements of Study 1 is that it enabled the exploration of results with behavioural indices of action updating. As outlined in previous Chapters, the PRP is argued to reflect a central bottleneck that is present in dual-task situations.

The presence of the PRP is argued to reflect the inability to select two responses simultaneously and may represent a limit in the cognitive resources available for decision making (Telford, 1931; Welford, 1952). If so, it would have been anticipated that pupil diameter for signal trials in the DT to be greater within- vs. post-bottleneck periods- reflecting increased mental effort as opposed to physical effort (which is consistent across signal trials in the DT). Although it may be argued that the central bottleneck demonstrates a strategy to reduce dual-task demands rather than a structural limitation *per se* (e.g. Meyer & Kieras, 1995, 1997a, 1997b; Schumacher & Lauber, 1999; although see Ruthruf et al., 2003), pupil diameter was not found to be related to other measures of DT performance (including DRT2 and the size of the bottleneck). Thus, although it is possible that the difference in pupil diameter on signal trials relative to no-signal trials in the DT may be due to physical as opposed to mental effort (e.g. Zénon *et al.*, 2014), this seems unlikely given the lack of difference between pupil diameter on signal trials across the contexts (as only signal trials in the DT requires the execution of an additional response). More work is needed to clarify the reason for this difference.

It is noteworthy that the mean pupil diameter across signal and no-signal trials within each context (with the exception of the DT; Figure 6.7) were found to be very similar. While increases in pupil diameter associated with cognitive demands are typically very small (Sirois & Brisson, 2014; van Steenbergen & Band, 2013; and may not be assoicated with the current task demands), the relationship could also be confounded by the slow reactivity of pupil dilation and subsequent constriction. Although many studies employ shorter inter-trial-intervals (ITIs) than used here (e.g. Chatham *et al.* (2012) used an ITI of 250ms vs. 500/1000/2000ms used here), the time for pupil diameter to return to baseline may not have been adequately accounted for. Indeed, Chatham *et al.* (2012) show pupil diameter takes 1,600ms (and longer) to return to baseline, and this time is likely to vary according to specific task demands and the duration of stimulus presentation (Beatty, 1982; Cavanagh *et al.*, 2014; Beatty & Kahneman, 1966; Kahneman *et al.*, 1967). Therefore longer ITIs may be needed in future work to fully delineate the association between pupil diameter and task demands in the context-cueing paradigm. Exploration of the time-course of pupil change across time within different tasks could also be of benefit in future studies, particularly where eye-trackers with greater temporal resolution than employed in the current study were

used (i.e. the eye-tracker used here had a sample rate of 250Hz, where eye-trackers with sample rates up to 1,000Hz are available).

Finally, although inconclusive, a striking finding was the negative relationship between self-report measures of task-related difficulty and frustration with pupil diameter in both the SST and DT after outlier exclusion (APP10.5.4). It was anticipated that increased cognitive demands would be associated with increased pupil diameter (e.g. Beatty & Kahneman, 1966; Kahneman *et al.*, 1967; Piquado *et al.*, 2010), but instead pupil diameter appeared to constrict with increased perceived effort. Similar findings have been observed under conditions of response inhibition in previous work. For example, pupil diameter has been found to decrease on no-go trials in the Simon task (Schacht, Dimigen, & Sommer, 2010). Given that that pupil diameter is often found to be correlated with other measures of autonomic arousal (including skin conductance, heart rate variability and respiratory responses; e.g. Bär, Schulz, Koschke *et al.*, 2016; Bradley, Miccoli, Escrig, & Lang, 2008; Daum & Fry, 1981; Kahneman, Tursky, Shapiro, & Crider, 1969; Schacht et al., 2010), this may be reflective of a slowing of the autonomic system associated with response conflict and response preparation - both of which are likely greater under SST relative to DT and IT conditions. However, this explanation does not account for the similar pattern of DT-related frustration and pupil diameter. Alternatively, the pattern of results could be associated with a change in physiological arousal associated with task uncertainty, as has been suggested in previous work (e.g. Yu & Dyan, 2005; Yu, 2012). Rather than mental effort *per se*, it has been argued that pupil diameter dynamically adjusts to facilitate evidence accumulation (Nassar, Wilson, Heasly & Gold, 2010). However, such top-down control of pupil responsiveness has been linked to the neurotransmitters acetylcholine and norepinephrine (Yu & Dyan, 2005; Yu *et al.*, 2012) – the origins and mechanisms of which are different to those hypothesised to underlie action control – i.e. GABAergic and glutamateric communication in the basal ganglia and thalamus (Figure 3.1; Albin *et al.*, 1989; Alexander & Crutcher, 1990; Nambu *et al.*, 2002). Thus, pupil diameter itself may not be a direct measure of the difficulty in implementing action updating in simple motoric tasks, such as those presented in the context-cueing paradigm. More work is required to substantiate the presence of these effects and the nature of the relationship between task demands and autonomic nervous system activity.

6.4. General discussion and conclusions

The aim of this Chapter was to establish whether differences in cognitive demands between the tasks comprising the context-cueing paradigm may help to explain the inconsistencies between the results yielded in Studies 1 and 2 from those identified in previous work (e.g. Chatham *et al., 2*012; Dodds et al., 2011; Erika-Florence *et al., 2*014; Hampshire, 2015; Verbruggen *et al., 2*010). A combination of objective and subjective measures appeared to provide conflicting results, yet, albeit indirectly[99], indicate that task demands may explain at least some of the functional disparity observed in the rIFG. Such work highlights the factors that need consideration when interpreting results from response inhibition research, particularly in the imaging domain.

Subjective ratings of task-related difficulty and frustration indicate that the SST is more demanding than the DT and IT. Although subjective measures rely on accurate assessment by participants, they are likely to confer greater sensitivity to assessment of cognitive effort than may be possible by objective measures (e.g. Garofalo & Lester, 1985; Gift, 1989; Jahedi & Méndez, 2014). These ratings may therefore be more useful than the psycho-physiological measures employed, where only very small changes in autonomic nervous system activity are expected to occur as a result of task demands (e.g. Sirois & Brisson, 2014; van Steenbergen & Band, 2013). If, as the self-report measures suggest, the SST is the more demanding and frustrating of the three tasks, then it is possible that the unique activity observed under conditions of response inhibition in Studies 1 and 2 reflects additional effort or frustration rather than an inhibitory system, and thus that the rIFG may not house a specific inhibitory neural module as indicated by previous similar work (e.g. Chatham *et al., 2*012; Dodds et al., 2011; Erika-Florence *et al., 2*014; Verbruggen *et al., 2*010).

If the SST is the more demanding task, then what exactly are these 'demands'? Given the error-likelihood and conflicting task instructions (i.e. respond with speed but stop where possible) associated with responding to the SST, it is likely a combination of error/performance monitoring and response conflict resolution processes. As outlined in Section 6.2.1, this interpretation is supported by the ACC and DLPFC activity observed under SST conditions. Furthermore, if the DT was the more demanding of the tasks, as

[99] As I do not correlate any of the measures explored here in relation the pattern of activity under different conditions with those observed in the fMRI data itself.

the cardio-respiratory analyses indicate, then activity in these regions would be expected to be greater relative to the SST, particularly given the role of the ACC in regulation of autonomic nervous system activity (Jennings *et al.*, 2002; Leech & Sharp, 2014; Matthews *et al.*, 2004; Van Boxtel *et al.*, 2005; Zhang *et al.*, 2012). Conversely, pupil diameter in the SST was found to be negatively (although inconclusive) correlated with task-related difficulty and frustration. Although the negative relationship opposes what was anticipated, I speculate that this may be associated with the particular demands in the SST.

Indeed, different physiological responses have been found to co-vary with task demands and correlations between psycho-physiological measures have been found in previous work (e.g. Carroll *et al.*, 1986; Kahneman *et al., 1*967; Siegle *et al.*, 2003; Zénon *et al.*, 2014). Here, cardiac responses across contexts may be confounded by the slowing of heart rate associated with response selection and preparatory demands and subsequent to task errors (Jennings *et al.*, 1990, 1992; Van Boxtel *et al.*, 2005; Van Boxtel & Van der Molen, 2001; Van Der Veen *et al.*, 2003), for which the likelihood is greater in the SST relative to the DT and IT (see Figures 6.1a and 6.5a). This interpretation would explain why no differences in cardio-respiratory and pupillometry measures were found between the SST and the IT, even though the SST requires the updating of an ongoing action plan. These findings may therefore be indicative of an overall slowing of autonomic nervous system activity under conditions of response inhibition - potentially as a result of elevated proactive control, increased error likelihood and associated response conflict.

While such an interpretation is intriguing it does not fit well with the similar pattern of pupil construction associated with increased task-related frustration in the DT - particularly, given the increase in pupil diameter observed on signal trials relative to no-signal trials in the DT. Further research is required to establish the nature of these relationships, with longer ITIs to fully ensure that trial-by-trial differences in pupil responsivity to task demands can be adequately detected (Beatty, 1982; Cavanagh *et al.*, 2014; Beatty & Kahneman, 1966; Kahneman *et al.*, 1967).

If the greater rIFG activity observed in relation to the SST, relative to DT, in Studies 1 and 2 is due to task demands, then why have opposite findings been reported in previous studies? The reasons for this are likely due to differences in the way in

which the SST and control tasks are implemented The differences in task demands between my own work and that of others is discussed in Chapter 2 (see Section 2.5).

The current study was subject to a number of limitations. As aforementioned, limited task-related changes in autonomic nervous system activity were expected (e.g. Sirois & Brisson, 2014; van Steenbergen & Band, 2013) and previous tasks that have successfully differentiated demands using these measures are arguably more challenging than those presented in the context-cueing paradigm (e.g. mental arithmetic computation, memory-tasks, driving and flying; e.g. Beatty & Kahneman, 1966; Kahneman *et al.*, 1967; Piquado *et al.*, 2010; Veltman & Gaillard, 1998). Additional indices of task difficulty may provide greater insights where the measures cited here provide inconclusive evidence (e.g. eye blinks as opposed to pupil diameter: van Bochove, Van der Haegen, Notebaert, & Verguts, 2013; heart rate variability as opposed to cardiac rate: Jennings *et al*., 1990). Furthermore, cardio-respiratory and pupillometry measures are notoriously noisy and may have clouded the potential differences between tasks. Additional work is also needed to establish whether the pattern of findings here correlate with region-specific %BOLD and to assess whether they are repeatable in MR conditions (as behavioural performance has been found to vary between MR and laboratory environments; Koch *et al., 2*003; van Maanen *et al., 2*015; Hommel *et al., 2*012; Koten *et al., 2*013; Assecondi *et al., 2*010; van Maanen *et al., 2*015).

Consequently, the self-report data indicate that inhibiting a response may be more demanding than updating a response or running an action plan to completion. As such, the rIFG activity established in Studies 1 and 2 may well be the result of task complexities or differential recruitment of a multiple demand cortex (in accord with Erika-Florence *et al.*, 2014; Hampshire, 2015; Hampshire & Sharp, 2015a, 2015b) as opposed to reflecting a specific inhibitory module. However, to fully elucidate whether task demands can account for rIFG activity future work must better match the dynamics of inhibitory and non-inhibitory control tasks. To this end, a novel task design is proposed in Chapter 7.

Chapter 7. Study 4

The stop signal task and the search for a comparable paradigm

7.1. Overview

As discussed in Chapter 6, the DT, as presented in the context-cueing paradigm, may not provide an adequate control for non-inhibitory processes that contribute to performance on the SST. Differences in error likelihood and response conflict across the tasks may contribute to differences in BOLD activity when such tasks are employed in imaging studies. In this chapter, I therefore propose a novel paradigm that aims to match the error profiles between a stop and control task, while also providing analogous measures of inhibitory and non-inhibitory action updating. I argue that such a paradigm would be a viable alternative to the standard SST, where evidence indicates that under certain conditions, measures of SSRT are unreliable due to violations of assumptions fundamental to their estimation (e.g. Bissett & Logan, 2014; Verbruggen & Logan, 2015). Test-retest reliability and variability in this novel paradigm and the standard SST are also discussed.

7.1.1. Unreliability of stop signal reaction time estimates

In the SST there is no overt response on successfully inhibited stop-signal trials. As such, the latency of the stop process must be estimated using the mean or integration methods (Logan & Cowan, 1984; see also Verbruggen & Logan, 2009a). These estimation methods are based on the independent race model (Logan & Cowan, 1984) that assumes both contextual and stochastic independence between stop and go processes. That is, the RT to go trials is unaffected by the presentation of stop signals and that trial-by-trial variability in no-signal (go) RTs are not affected by trial-by-trial variability in SSRT (Logan & Cowan, 1984). The independence assumption has received much support, including evidence that these processes are not sensitive to dual-task interference (as present in the psychological refractory period; Sella, Bonato, Cutini, & Umiltà, 2013; Yamaguchi, Logan, & Bissett, 2012; but see Levy, Pashler, & Boer, 2013). A primary prediction of the independent race model is that mean RTs to go

trials should always be longer than mean RTs to unsuccessful stop trials. This is because the former represents a mean based on all go trials, whereas the latter only represents those RTs that are fast enough to 'win' the race against the stop process (Figure 7.1; Logan & Cowan, 1984; see also Verbruggen *et al.*, 2009a). However, longer stop-respond RTs, relative to go RTs, have been found in saccade countermanding tasks (Gulberti, Arndt, & Colonius, 2014; Ozyurt, Colonius, & Arndt, 2003). In addition, the efficacy of this model has been questioned after recent findings indicate dependency between the stop and go processes under selective-stop conditions (Bissett & Logan, 2014; Verbruggen & Logan, 2015; see also De Jong *et al.*, 1995). Specifically, Verbruggen & Logan (2015) were able to substantiate the presence of an interaction between stop and go processes by manipulating the complexity of stimulus-response mapping in a selective-stop task. When stopping-rules were held constant across the task, Verbruggen & Logan (2015) found reliably faster signal-respond RTs (i.e. RTs to unsuccessful stop signals) relative to go RTs. This finding is illustrated in Figure 7.2 (left panel) and demonstrates independence: the signal-respond RT distribution was found to lie reliably to the left of the go RT distribution. Conversely, when the stop-rule was frequently altered throughout the task, overlaps between these distributions were observed (Figure 7.2, right panel) indicating interaction between the underlying stop and go processes[100] (although also see Logan *et al., 2*014). Verbruggen & Logan (2015) argue that this interaction is the result of competition between these processes for limited capacity resources that only become evident when demands on the system maintaining rule-based performance are high[101]. The possibility of interaction between the stop and go processes violates the independence assumptions of the independent race model. Consequently, estimates of SSRTs, which rely on these assumptions, are rendered unreliable (see also De Jong *et al.*, 1990).

[100] Note. It is possible that this pattern of results could be explained by failures of inhibition independently of the go process (e.g. lapses of attention; Hampshire & Sharp, 2015). However, the independent race model does not account for such explanations. Alternative models of decision making more generally have been advocated where such discrepancies are accounted for (e.g. evidence accumulator models; see Teodorescu & Usher, 2013; Winkel, Keuken, van Maanen, *et al., 2*014; Forstmann, Ratcliff & Wagenmakers, 2016).

[101] Although note, violations of the independence assumptions were found for some subjects in both conditions.

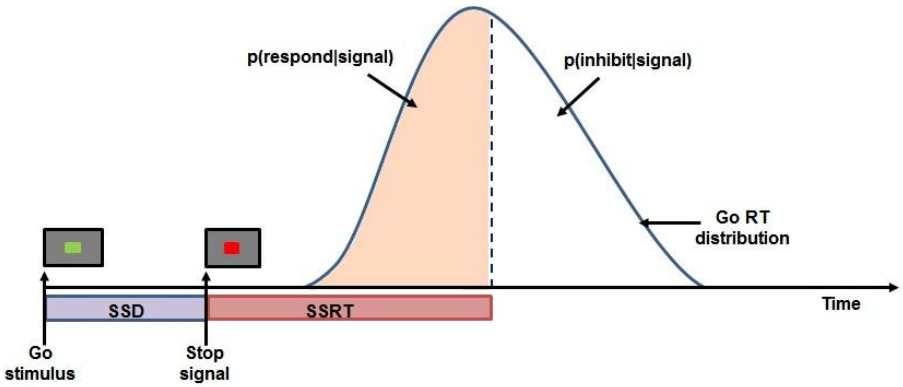


Figure 7.1. Graphic representation of the independent race model (Logan & Cowan, 1984). The probability of incorrectly responding to a stop signal (*p*(respond|signal) is represented by the pink area- that is, under circumstances where the go process is fast enough to evade inhibition. The model assumes that the mean reaction time (RT) to unsuccessfully inhibited stop signal trials is shorter than the than the mean RT to go trials: the former is represented by the mean of those trials that were fast enough to escape inhibition (those responses to the left of the vertical dashed line), whereas the latter is represented the mean of the entire goRT distribution. The image demonstrates the onset of go and stop processes. **SSD**=stop signal delay; **SSRT**= stop signal reaction time. Image adapted from Verbruggen & Logan (2008).

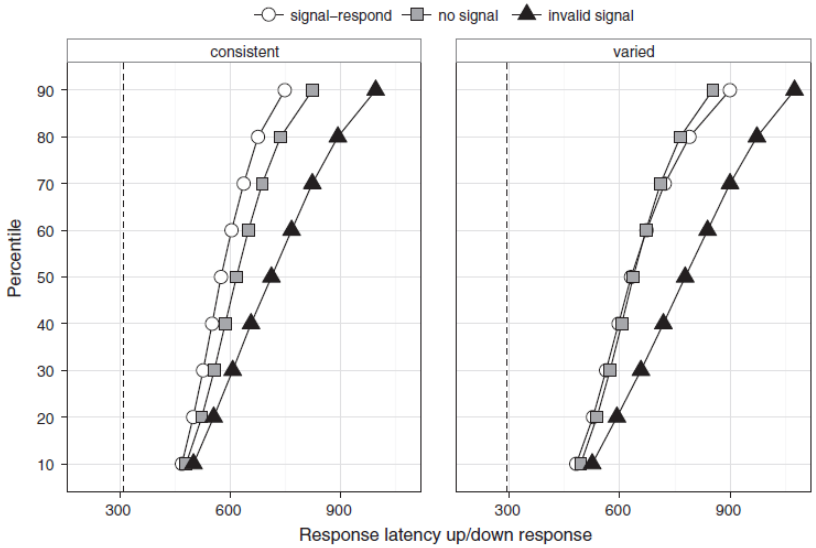


Figure 7.2. Results from Verbruggen & Logan (2015) depicting percentiles for mean reaction times to signal-respond, no-signal and invalid-signal (i.e. signals that did not require inhibition) trials presented under consistent and varied stop-rule conditions. When the stop rule was consistent (left panel), the distribution of signal-respond RTs is consistently to the left of the no-signal distribution, indicating that RTs on unsuccessful stop trials were reliably shorter than on no-signal trials. However, when the stop rule was varied (right panel), the signal and no-signal RT distributions overlapped, indicating interaction between their underlying processes.

Here, SST data for studies 1-3 cited in this thesis were explored for violations of the independence assumptions[102]. As the model predicts, mean signal-respond RTs were reliably shorter than mean go RTs for each of these studies (Study 1: $t_{(29)}$=9.82, $p_{.0167}$<.001, BF=1.01^{e+8}; Study 2 (Sham data): $t_{(29)}$=6.27, $p_{.05}$<.001, BF=22852; Study 3: $t_{(29)}$=9.11, $p_{.025}$<.001, BF=2.1^{e+7}, where *p*-value subscripts correspond to the α level used for comparison after Holm-Bonferonni correction; Aickin & Gensler, 1996). However, exploration of the corresponding RT distributions revealed a degree of dependency evident in Study 2 (illustrated in Figure 7.3b). The independent race model posits that while stop signal and go RT distributions share a common minimum, they later diverge (Logan & Cowan, 1984). While the overlap in distributions appears to occur initially, this extends to the 20th percentile. This demonstrates dependency between the stop and go processes as the mean RTs to unsuccessful stop trials are prolonged relative to the mean go RTs. Furthermore, subtraction of mean go RTs from unsuccessful stop RTs for each participant signifies that a number of participants across all studies responded more slowly on unsuccessful stop trials relative to go trials (this was most evident in Study 2 even though the sample sizes were matched across studies; Figure 7.2d). This demonstrates that shared capacity for resources may manifest in even the simplest stop-signal paradigms where stop-rules are consistent (although note a review of studies by Verbruggen & Logan, 2009b, found the majority of previous studies that utilise the SST do comply with independence assumptions). Verbruggen & Logan (2015) recommend the exclusion of participants who violate assumptions as the resulting SSRT estimates are unreliable. As such, I re-analysed all data concerning SSRTs from previous chapters (APP10.6.2), subsequent to exclusion of these participants. This was found to have minimal effect on the interpretability of results, potentially owing to the few violations observed.

[102] Note that for Study 2 only data acquired during sham cTBS conditions were explored.

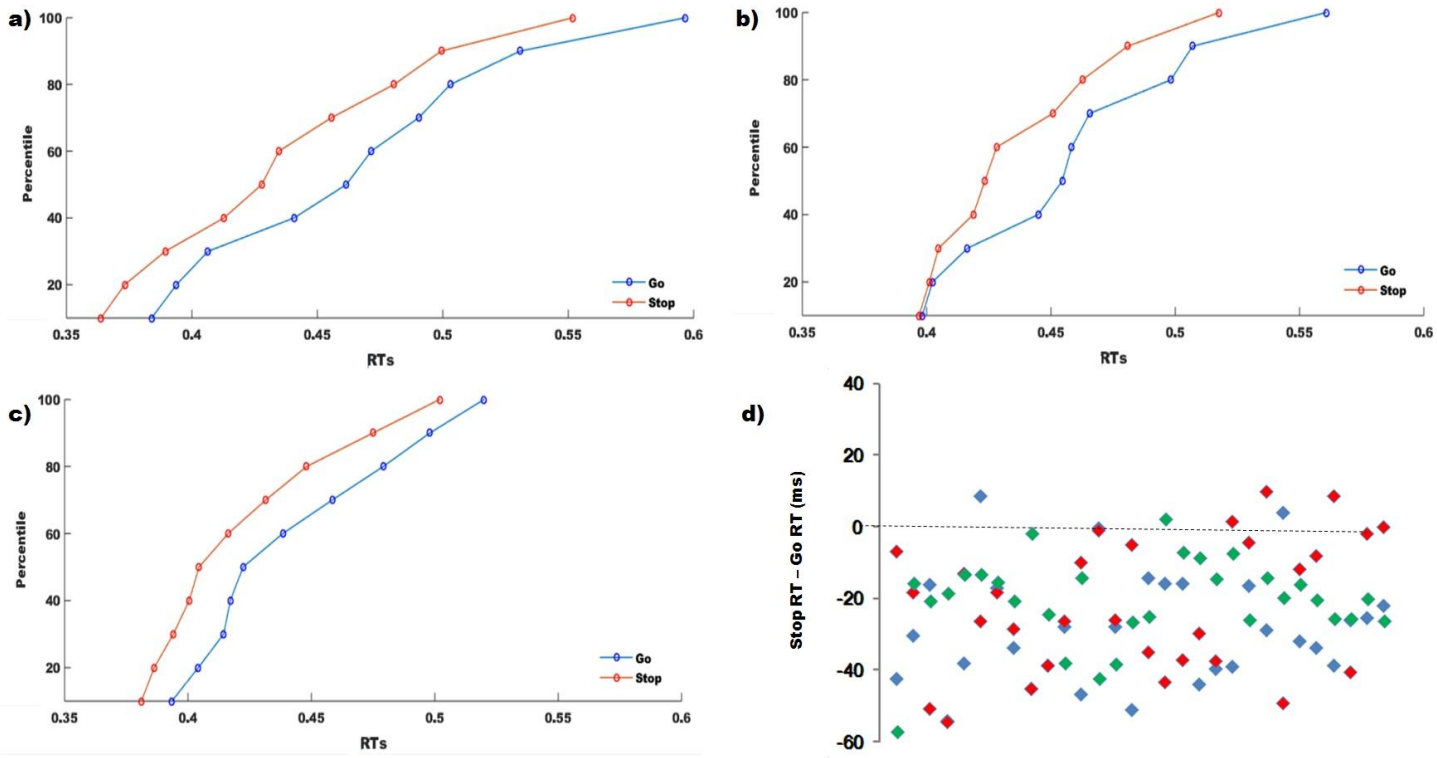


Figure 7.3. Distributions of reaction times to stop-signal (red) and go (blue) trials in the SSTs used in studies **(a)** 1, **(b)** 2, and **(c)** 3. Interaction between the stop and go processes is evident at the 20th percentile in study 2 **(b)**. Panel **(d)** illustrates the distribution of difference scores computed by subtracting reaction times to go trials in the SST from RTs corresponding to unsuccessful stop signal trials for Study 1 (blue), Study 2 (red) and Study 3 (green). Symbols above the central dashed line indicate data points where mean response times to unsuccessful stop trials were longer than go trials. Data points below the dashed line denote participants whose mean go reaction times were longer than unsuccessful stop reaction times.

The potential for dependency between stop and go processes has begun to be recognised in revised race models (e.g. the general/special race model, Logan *et al.*, 2014; and the interactive race model, Boucher, Palmeri, Logan, & Schall, 2007), however at least some degree of independence is still assumed (see Logan *et al.*, 2014 for a discussion). Simulations of RT distributions have established that even small violations can be problematic where the integration method is used to estimate SSRTs (Band, van der Molen, & Logan, 2003; see also De Jong *et al.*, 1990). Alternative methods of estimation are available, but all rely on the independence assumptions of the independent race model (e.g. Colonius, 1990; De Jong *et al.*, 1990; Matzke, Dolan, Logan *et al.*,2013; Mayse *et al.*, 2014; Teichert & Ferrera, 2015). Such issues can be overcome by the direct measurement of stop latencies using continuous rather than discrete SSTs.

7.1.2. Continuous paradigms

Standard SSTs involve the execution and countermanding of discrete key presses. However, the cessation of ongoing responses has been explored in speaking (Ladefoged, Silverstein, & Papcun, 1973), type-writing (Logan, 1982), finger-tapping (Teichert & Ferrera, 2015), scribbling (Sosnik, Shemesh, & Abeles, 2007) and target connection tasks (Sosnik, Chaim, & Flash, 2015). Responses with different effectors including arm and wrist movements (e.g. Brunamonti, Ferraina, & Paré, 2012; Mirabella, Pani, & Ferraina, 2011), or the application of force by the fingers (De Jong *et al.*, 1990, 1995), have also been investigated. However, many of these studies employ discrete methods of SSRT estimation (e.g. De Jong *et al.*, 1995, 1990), which inherently assume independence between the stop and go processes. A series of pursuit tasks that confer direct measurement of stop latencies (and thus avoid reliance on independence assumptions) have been developed by Morein-Zamir *et al*. (Morein-Zamir, Chua, Franks *et al.*, 2007; Morein-Zamir, Nagelkerke, Chua *et al.*, 2004; (Morein-Zamir, Nagelkerke, Chua *et al.*, 2006; Morein-Zamir & Meiran, 2003).

Examples of the paradigms employed by Morein-Zamir *et al.* are illustrated in Figure 7.4. Typically these tasks require either manual tracking of objects using a mouse (Figure 7.4a), executing a single key-press whilst a target is in motion (Figure 7.4b), or the pursuit of moving objects via the application of force (Figure 7.4c). The outright stopping of a moving target instructs participants to stop their responses. Stop

latencies are measured as the time between signal onset and the time the participant stops their response. The use of mouse-tracking (Morein-Zamir & Meiran, 2003, Figure 7.4a) provides an additional measure of inhibitory control: the Euclidean distance between the cursor position at signal onset and the cursor position at the point of outright stopping. Dissociation between stop RTs and tracking performance have been found, with the former influenced by perceptual task demands (including the modality of signal presentation) and the latter influenced by motor task demands (including the speed of tracking). Continuous SSRTs have also been found to be susceptible to stimulus-response compatibility (Sharon Morein-Zamir et al., 2006) and signal presentation probability (Morein-Zamir *et al.*, 2007) consistent with findings in the standard SST (e.g. Castro-Meneses, Johnson, & Sowman, 2015; Kramer, Humphrey, Larish *et al.*, 1994; Ramautar, Kok & Ridderinkhof, 2004; Ridderinkhof, Band, & Logan, 1999; van den Wildenberg & van der Molen, 2004; van der Schoot, Licht, Horsley, & Sergeant, 2005; Verbruggen, Liefooghe, Notebaert, & Vandierendonck, 2005; Verbruggen, Liefooghe, & Vandierendonck, 2004; Vink *et al.*, 2015).

The utility of continuous tasks and comparison with a standard SST were demonstrated in a study exploring inhibitory impairments in children with attention-deficit-hyperactivity disorder (ADHD; Morein-Zamir, Hommersen, Johnston, & Kingstone, 2008). These children were found to be impaired on both a pressure-response pursuit task and a standard SST compared to age and gender-matched controls. Performance on these tasks was found to correlate. Additionally, Morein-Zamir *et al.* demonstrated that children with ADHD exhibited more trial-by-trial variability in continuous inhibition tasks relative to healthy controls. It is not possible to gauge such trial-specific information in a classic SST due to the estimation of SSRTs over numerous trials (see also Scheres, Oosterlaan, Guerts *et al.*, 2004; Scheres, Oosterlaan, Swanson *et al*., 2003).

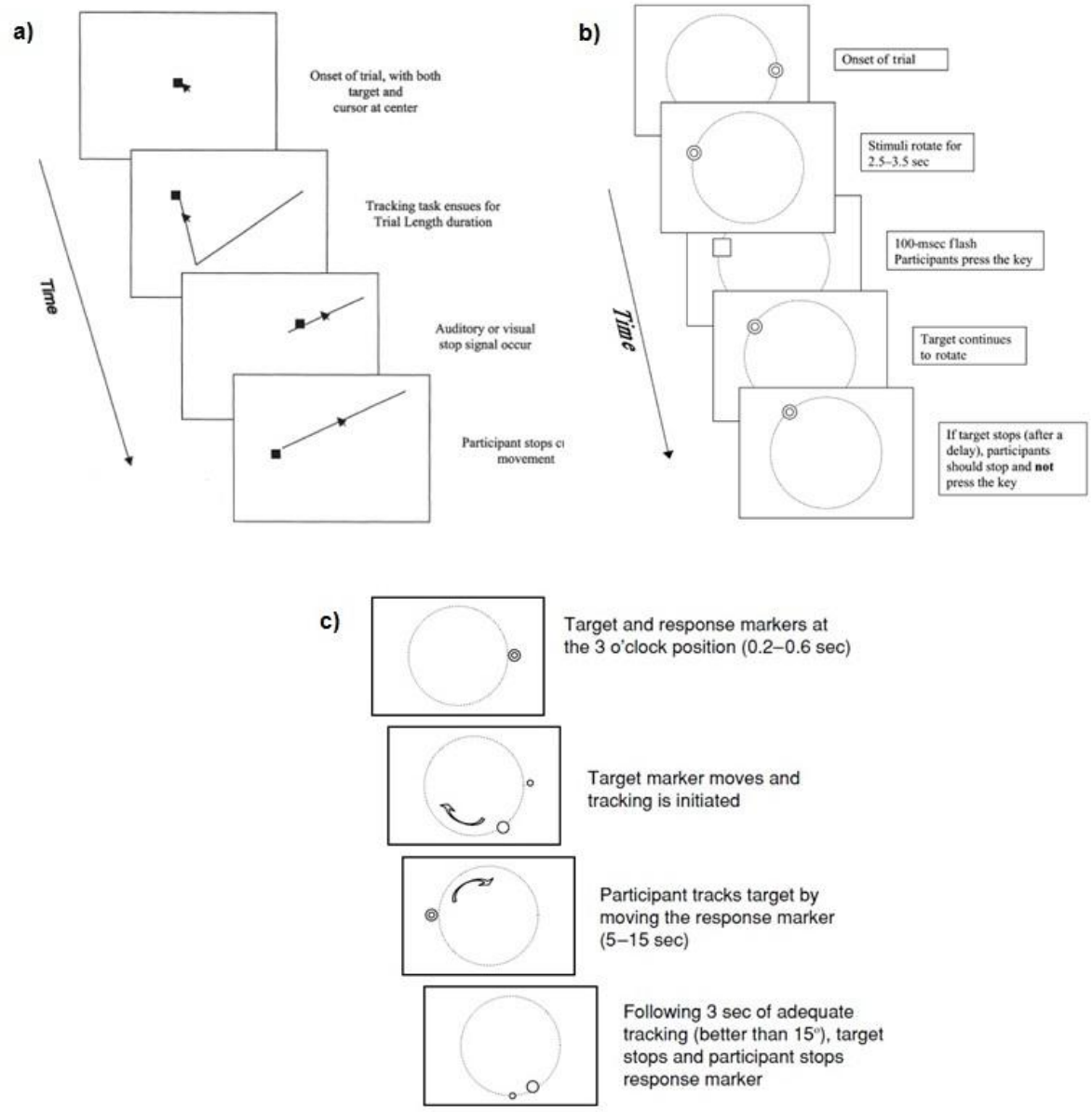


Figure 7.4. Summary of pursuit tasks developed by Morein-Zamir *et al*. **(a)** From Morein-Zamir & Meiran (2003). Outlines a tracking task in which participants were instructed to track a moving object on the screen using a mouse. Visual or auditory stop signals were presented and the speed and duration of the tracking manipulated. **(b)** From Morein-Zamir *et al.* (2004). Illustrates a pursuit task in which participants were instructed to press a button while a target was moving in a circular direction and stop as soon as the object stopped. **(c)** From Morein-Zamir *et al.* (2006). Illustrates a pursuit task whereby participants had to apply force in order to move a response marker. Participants were instructed to move the response marker in line with a moving target marker. Speed of the response marker was manipulated by varying the force applied to the button; the more force applied, the faster the response target moved. Participants were instructed to stop applying force as soon as the moving target stopped.

7.2. Task development

To reiterate, the aim of this chapter was to develop a novel paradigm that allows us to explore inhibitory and non-inhibitory action updating processes through the use of analogous updating measures. Given the concerns underlying the dependency between the stop and go processes in standard SSTs, continuous response paradigms appear a suitable alternative. Their use enables direct measurement of stop latencies, by-passing the requirement to base estimations on mathematical models. Data collection efficiency is also enhanced because trial-specific measurement avoids the minimum requirement of 50 signal trials for reliable SSRT estimation as in the SST (Verbruggen *et al.*, 2013). Although the work by Morein-Zamir *et al.* is compelling there are a number of obstacles that I have attempted to overcome in the current work.

Firstly, in Morein-Zamir *et al*.'s (2004) pursuit task participants are required to apply force to a key that had to be removed when stopping was required. This reduction in applied force could be construed as the execution of an additional response (i.e. by moving a finger away).[103] Secondly, such tasks are not readily usable without complex programming and equipment (e.g. force detector). Mouse-based designs are easier to implement and most participants are familiar with their use (see also Hehman, Stolier, & Freeman, 2015; Schneider, van Harreveld, Rorreveel *et al.*, 2015). Thirdly, tracking a randomly moving object, as per Morein-Zamir & Meiran's (2003) mouse-based task, requires additional monitoring and updating requirements. Such control demands confound measurement of inhibitory and non-inhibitory processes and their associated proactive control tendencies. Less complex paradigms have been employed in decision-making research for the assessment of speed of object categorisation (Dale, Kehoe, & Spivey, 2007; Freeman, Ambady, Rule, & Johnson, 2008; Freeman & Ambady, 2009), target selection (Song & Nakayama, 2008), learning (O'Hora, Dale, Piiroinen, & Connolly, 2013) and responses to different motivators (Dshemuchadse, Scherbaum, & Goschke, 2012; Sullivan, Hutcherson, Harris, & Rangel, 2015). Adaptation of these paradigms has made it possible to measure action updating under different conditions.

[103] Although note, Morein-Zamir *et al.* (2004) cite the work of Naito & Matsumura (1996) who found no differences between response times when releasing pressure and withholding a prepotent response and argue that as stopping is the consequence of the action it is unlikely participants perceive this as a different action plan.

7.2.1. Task design

In the proposed stop/change task, participants were required to use a mouse to move a cursor from the bottom of the screen to an upper right or upper left target depending on the direction of an arrow cue (Figure 7.5). To tap into inhibitory and non-inhibitory action-updating processes, participants were required to occasionally stop or change their responses upon presentation of a signal (screen background changing colour). Note that an empirical question posed by the current study was whether non-inhibitory action updating (as measured via the change condition) could occur in the absence of slowing or stopping[104].The stop/change task was also designed to overcome other issues with the context-cueing paradigm, including the mismatch of error likelihoods and response conflict across the tasks. Importantly, the change in cursor trajectory does not involve the execution of an additional response as required in the DT, but still requires participants to update an ongoing action plan. In addition, limiting the direction of the change condition renders the task more comparable to the stop task as there is only one way to update the action in response to a signal. Such design considerations minimise the differences between stop and change conditions.

[104] Whether stop and stop/change inhibition processes are supported by the same mechanism is a topic of much debate in the discrete stop/change task literature and consequently remains unclear (Boecker, Gauggel, & Drueke, 2013, for a review).

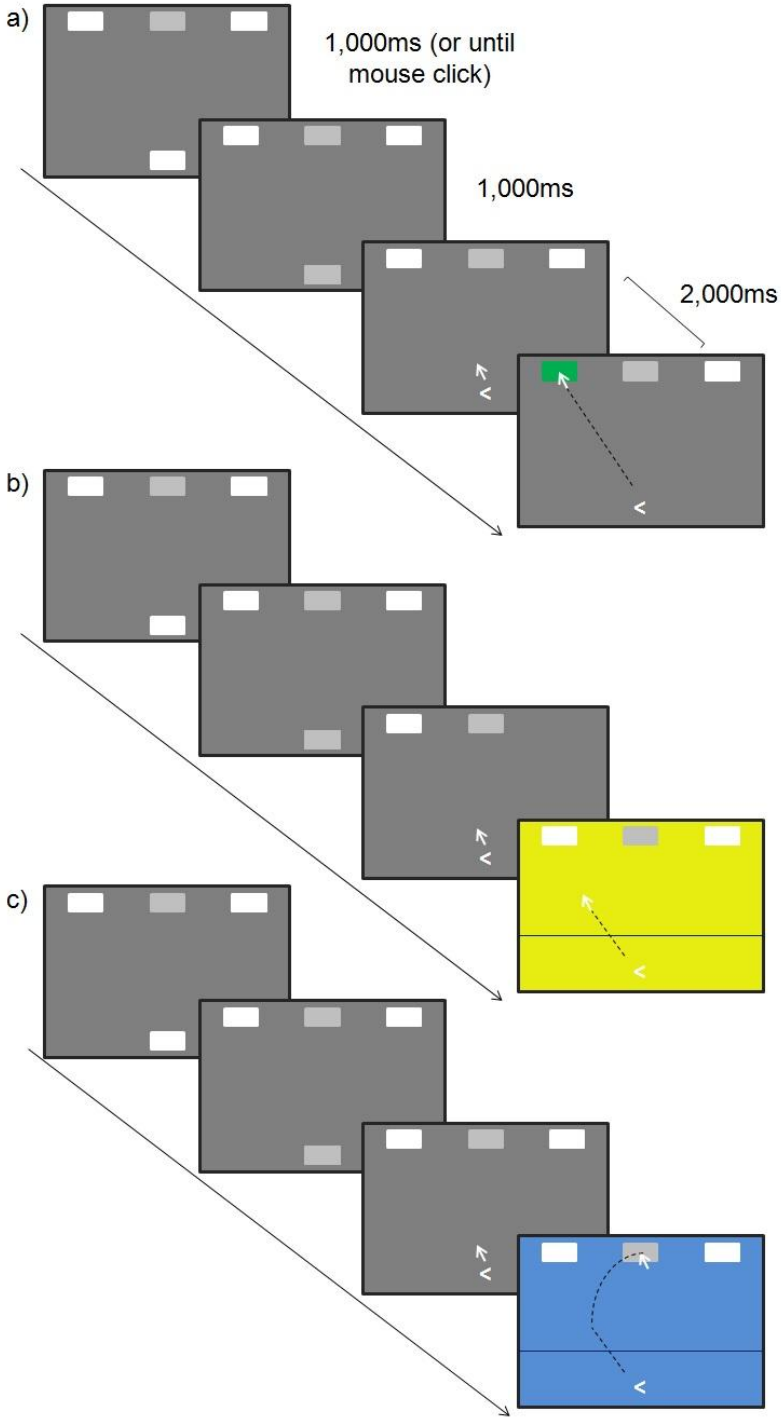


Figure 7.5. Illustration of the conditions comprising the stop/change task; **(a)** go, **(b)** stop, and **(c)** change. On all trials participants were instructed to move the cursor towards the target to which an arrow cue was pointing as fast and accurately as possible. On successful go trials the target turned green indicating the end of the response. On stop and change trials, the background changed colour once the cursor was moved beyond a pre-set distance based on the Y-axis (here, depicted by the horizontal lines – note these lines were not presented on the screen). On stop trials, participants were instructed to stop moving the cursor. On change trials, participants were instructed to move the cursor away from the target and towards a top centre change location. Note that only one signal type (either stop or change) occurred in any one block. On both stop and change trials, participants were instructed to try and update their response as quickly as possible and to avoid hitting the target with the cursor. The dashed lines illustrate anticipated mouse trajectories.

Given the requirement to move the mouse along the distance of the screen, mouse movement was adjusted so that it moved 100 dots per inch (see Section 7.3.2.1) so that participants would have sufficient time to successfully update their responses before reaching the top of the screen. This resulted in a whole arm extension, as opposed to a typical wrist movement required to orient the mouse. Although previous work has suggested that long movements are difficult to modify (e.g. Henry & Harrison, 1961[105]), arm, wrist and finger responses have been found to be governed by a common inhibitory mechanism (e.g. Brunamonti, Ferraina & Paré, 2012). Similarly, the inhibitory process underlying the stopping of actions underway (as in continuous paradigm), compared to those to-be-executed (as in the SST), has been argued to be supported by a common mechanism (Logan & Cowan, 1984; Morein-Zamir *et al.*, 2004). The added advantage of the use of continuous paradigms is that it allows the researcher to be sure that participants are actively executing a response that requires cancellation as opposed to simply deciding whether to respond or not as might happen in the SST (Shenoy & Yu, 2011), as well as the direct measurement of latent processes, which otherwise have to be inferred in the SST.

The current study also aimed to compare stop and change responses as acquired via the mouse-based (continuous) stop/change paradigm with those acquired from a key-press (discrete) stop/change paradigm (allowing comparability with previous work). In effect there were four separate tasks: continuous stop, continuous change, discrete stop and discrete change. Validation of response inhibition itself was sought via the inclusion of a standard SST. Collectively, the incorporation of these separate tasks enabled the comparison of action updating latencies and distances across different paradigms and response effectors. As mentioned, I was also interested in determining whether participants could change their response in the absence of inhibition; that is whether it was possible to establish a measure of action updating without contamination from inhibitory processes.

[105]Initiation and execution of long complex action plans are argued to largely ballistic and therefore difficult to modify.

7.3. Methods

7.3.1. Participants

Twenty four participants (5 male) aged between 18 and 30 years (*M*= 20.71, *SD*=3.33) completed the study[106]. All were right handed, had normal or corrected-to-normal vision and had normal colour vision. The study received ethical approval from the School of Psychology, Cardiff University. All participants provided informed consent and were awarded course credits for their time.

7.3.2. Behavioural tasks

Participants each completed three separate tasks: (1) a continuous stop/change task, (2) a discrete stop/change task and (3) a standard SST. Note that stop and change conditions were presented in separate blocks for the stop/change tasks. All tasks were programmed in Psychophysics toolbox in MATLAB (www.psychtoolbox.org; Mathworks, Natick,MA; Brainard, 1997) and presented on a screen with resolution of 1024 x 768 pixels and refresh rate set to 60Hz. Task-specific details and study procedure are outlined below.

7.3.2.1. Stop/change task

For both the continuous and discrete versions of the stop/change task participants were instructed to move a cursor from an initial start location at the bottom of the screen to either a left or right upper target depending on an arrow cue presented at the beginning of each trial (see Figure 7.5.). For go trials, participants were instructed to move the cursor towards the relevant target as fast and as accurately as possible, ensuring one smooth linear movement without adjustments in speed. If the cursor successfully met the correct target, the target turned green. Participants were asked to hold the position of the cursor until the start of the next trial (indicated by a change in colour of the start

[106] N was based on the number of participants required to ensure full counterbalancing of task order (SST, continuous task, discrete task), order of stop or change conditions within continuous and discrete stop/change tasks and colour-signal mapping (see Section 6.3.2.1).

location from grey to white, Figure 7.5). This was to ensure that no additional response updating would occur before the start of the next trial.

Signals were presented on a third of trials as indicated by a change in colour of the screen background (either blue or yellow; one colour per condition and counterbalanced across participants). Participants were instructed to either stop or change the direction of their movements on presentation of a signal depending on the task condition. In the stop condition, participants were instructed to stop moving the cursor as fast as possible after a signal appeared. In the change condition, participants were instructed to move the cursor towards an upper central change location, ensuring as smooth a transition as possible, limiting any adjustment in the speed of movement (including slowing and stopping). Signals were presented at different distances along the screen Y-axis. To prevent expectations and the adoption of proactive response strategies, three distances were used. Signals appeared as soon as the cursor reached 20%, 40% and 60% of the distance between the start and target locations (corresponding Y-axis co-ordinates: 566, 434 and 303, where Y=0 at the top of the screen). These distances were established during piloting and provided instances where participants could easily stop/change cursor movements and others where this was more difficult.

Signal onset distances (SODs) applied to the Y-axis only. It was anticipated that this would minimise the distances between signal onsets and target position between participants. Greater variability would be likely if the Euclidean distance was used as variability in motion along the X-axis is likely between participants, reducing the comparability of task difficulty. Trial order, direction of cue and SODs were randomised, but occurred with equal probability in each block. In an attempt to minimise the amount of slowing/stopping before a change response on change trials, task conditions were blocked. A block design also better matches the context-cueing paradigm employed in previous chapters as only one signal is presented (and therefore acted upon) in any one block. A block design is also useful for exploring proactive response strategies. In the stop/change tasks, order of stop or change blocks, and corresponding signal colours were maintained within a participant, but counterbalanced across participants. Figure 7.6 illustrates the size of start, target and change locations and their position (in pixels) as presented on the screen. The maximum response time for the cursor movement was 2,000ms.

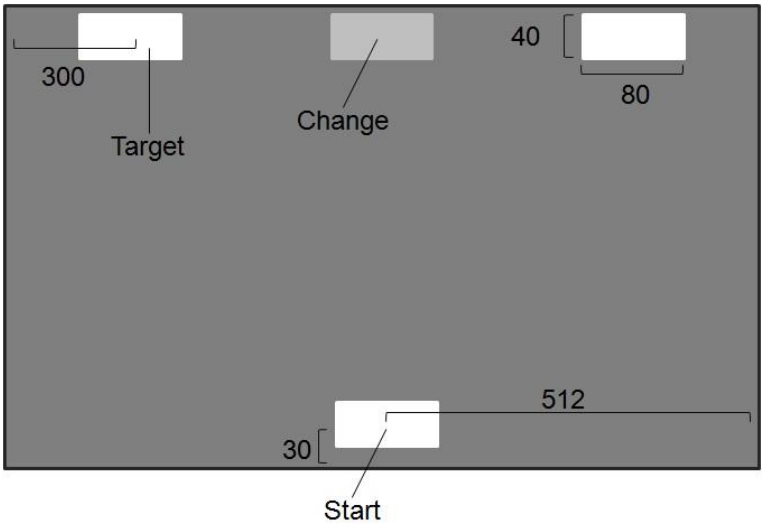


Figure 7.6. Illustration of position of start, target and change locations in pixels. All locations were represented by 80 x 40 pixel rectangles. Target locations were centred 300 pixels away from the horizontal limits of the screen and the change and start locations over the centre of the X-axis. For comfort, the start location was centred 30 pixels away from the bottom of the screen along the Y-axis

For the continuous stop/change tasks participants controlled cursor movement with a Razer DeathAdder mouse (Razer Inc, USA), set to 100 dots per inch in both the X- and Y-axis with a polling rate of 125Hz (Windows XP mouse sensitivity set to 5/11). Cursor position (in pixels) was sampled each screen refresh (1/60Hz). A standard keyboard was used to make responses in the discrete stop/change task. To move the cursor participants were required to hold either the left arrow key (←) or right arrow key (→) with either their right index or right ring fingers, respectively. Participants were to maintain their response until the cursor reached the target on go trials, or a signal was presented. Speed of cursor movement was computed individually for each participant and corresponded to the mean velocity (along the Y-axis) per sample on *continuous* go only trials (see study procedure, Section 7.3.3). On stop trials, participants were to release the key as soon as possible after the signal was presented. On change trials, participants were instructed to press the up arrow key (↑), using their right middle finger, as fast as possible after the signal was presented. The up arrow key was to be pressed until the cursor met the change location.

At the beginning of each trial, the start location appeared white. This appeared for 1,000ms in the discrete task, but was observed in the continuous task until a mouse click was made. This provided participants the opportunity to move they mouse to a comfortable location before starting the trial. The white start location turned grey for

1,000ms before the arrow cue was presented. The cursor position was re-set to the centre of the start location at the beginning of each trial in both continuous and discrete tasks.

7.3.2.2. Stop-signal task

The version of the SST employed here is largely in line with that used in previous chapters. Participants were required to respond to the direction of left and right white arrows (presentation time=1,250ms) as fast and as accurately as possible. Responses were made using the 'j' and 'k' keys on a standard keyboard with participants' right index and right middle fingers, respectively. Participants were required to stop their response if presented with a signal (the white arrow turning black for 250ms). Fixation crosses were presented for 1,000ms during the ITI. Stop signal delays (SSDs) were dynamically tracked throughout the task for each participant. Initial SSD was set to 250ms, and was increased by 50ms if participants successfully withheld their response and decreased by 50ms if participants failed to withhold their response. The minimum possible SSD was set to 50ms and the maximum possible SSD set to 1,000ms, to ensure the task was maintained as a SST (as opposed to a go/no-go task) and the signal was presented in its entirety. Stimulus direction and signal presentation was randomised, but occurred with equal probability within each task block. Participants were instructed to try not to slow their responses to enhance their chances of stopping successfully.

7.3.3. Study procedure

Participants completed 8 blocks of 36 trials (of which 33.33% were signal trials) per task. Task order was counterbalanced across participants. Participants were provided a 5,000ms break after completion of each block and a longer break (of unspecified duration) after every 4 blocks of each task. Task-specific instructions (see APP10.6.3), demonstrations and practice were provided prior to the experimental blocks.

Specifically, prior to completing either the continuous or discrete stop/change tasks participants completed a short block (18 trials) of continuous go only trials to practice the required mouse movements. In addition, participants were required to complete a standard block of continuous go only trials until they performed with

accuracy of 85% or above. The mean velocity (rounded to the nearest whole number; computed as the change in Y-pixels/time) was used to set the speed of cursor movement in the discrete stop/change tasks for each participant. Participants were also required to complete short blocks (18 trials) of the SST, prior to the experimental blocks. In the first block, to emphasise speed of responding, participants were instructed to ignore the presence of the signal and to respond only to the direction of the arrows as fast and as accurately as possible. This was to provide participants experience of the task, but with an emphasis on speed of responding. In the second block, participants were provided standard instructions (i.e. to respond to the direction of the arrow as fast and as accurately as possible, but to try and withhold their response upon presentation of a signal). No other training requirements were formalised, and participants practiced each task until they reported feeling comfortable with responses and instructions. Training data was not analysed.

At the end of every 4 blocks, participants were asked to rate how difficult and frustrating they found each of the tasks. Rating scales were the same as those used in Study 3 (Section 6.3.2.1.4).

7.3.4. Statistical analysis

Computation of dependent variables (DVs) differed between the stop/change and the standard SST. Task-specific calculations are detailed below. DVs were calculated separately for the initial 4 and last 4 blocks of each task and averaged for analysis. Analyses were conducted using custom-written Matlab (Mathworks) scripts, SPSS (version 20; Armork, NY: IBM Corp.) and JASP (Version 0.7.1.12, Windows XP; JASP team, 2016)[107]. To establish whether there were relationships between DVs, both within and between tasks, a series of difference and correlation analyses and their Bayesian equivalents were conducted (Rouder *et al.*, 2009, 2012; Wetzels & Wagenmakers, 2012). Data screening was as presented in Section 2.3.3. The results presented here include parametric tests with no outlier exclusion. Results with outlier exclusions and for non-parametric tests, where applicable, are reported in APP10.6.4. Inconsistencies between results are discussed.

[107] For Bayesian correlation analyses, the Matlab scripts supplied by Sam Schwarzkopf (http://sampendu.wordpress.com/bayes-factors/) were used to set a JZS prior (as opposed to the Jeffrey's prior offered by JASP).

7.3.4.1. Stop/change task analysis

In the stop/change task the velocity of cursor movement was calculated as:

$$Velocity = \frac{change\ in\ y\ coordinates}{time}$$

where time was equivalent to the sample-rate (1/60Hz). Velocity was measured across Y-coordinates only to minimise the differences in cursor speed between the continuous and discrete conditions (where the latter was set according to the former; see Section 7.3.3) and to ensure comparable calculation of baseline measures of velocity on continuous signal trials (see below). Greater variability was likely if Euclidean distance, as opposed to change in Y-coordinates only, was used due to the variability in mouse movement across participants.

On all trials, the start of motion was considered the point where positive velocity was found on two or more successive samples. The first 3 samples (50ms) from this point were excluded from all analyses to account for acceleration of movement. On go trials, the end of movement was considered the first sample where the lower boundary of the target was exceeded (i.e. Y<40). Go trial errors included: (1) Intermittent or outright stopping of movement for one or more samples before the target was reached[108]; (2) Missed targets (the bounds of the targets were extended during analysis to partially account for minor misses; see Figure 7.7 for acceptable boundaries and rationale); (3) If X-axis movement was towards the incorrect target[109] (in the discrete task, this applied to all samples, whereas in the continuous task this applied to the first three samples; see Figure 7.7); (4) No movement made for the duration of the trial.

[108] Note a 0 change in Y-coordinates between samples had to also be met with a 0 change in the X-direction on the same sample. This is because on occasion (due to the angle of the movement towards the target) movement may only occur in one direction.

[109] Moving in the incorrect direction may involve additional updating confounds. Such responses were expected to more likely at the beginning of the trial, where pre-emptive responses may be made.

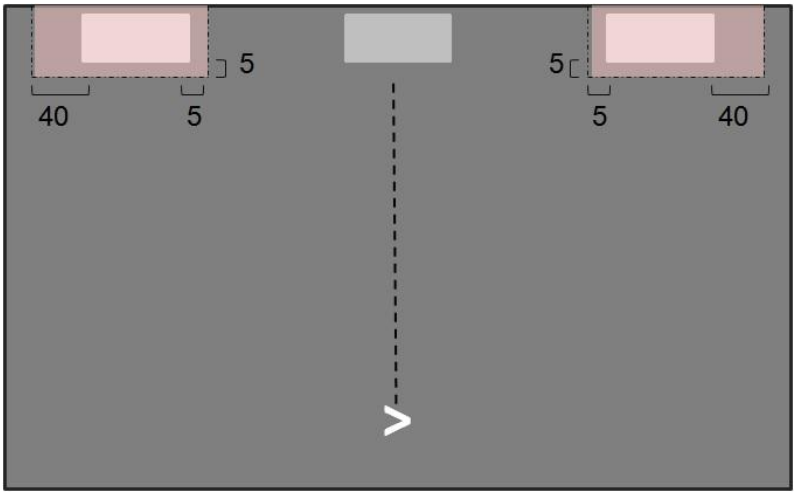


Figure 7.7. Illustration of the acceptable X-coordinate boundaries for each target to partially account for missed responses. Five pixels were added to the lower bounds of the target to partially account for premature stopping of movements before the target was reached. Forty pixels were added to the outer horizontal limits of each of the targets (closest to the edge of the screen) and 10 pixels were added to the inner limits of each of the targets (closest to the change location) to account for partial misses in moving the cursor within the target. A smaller boundary was applied to the inner boundaries of the targets to prevent incorrect change responses being considered correct go responses. The central dashed line represented the centre of the X-axis and is the boundary that was used to detect if participants were moving in the incorrect direction on continuous trials (either on go trials or prior to signal onset). Due to natural hand movements, some participants moved in the opposite direction between samples. However, to be noted as incorrect, the cursor had to be moving in the incorrect direction over the first three samples in a trial and these movements also had to be made to the wrong side of the screen as separated by this X-boundary.

RTs and distances for each measure were computed *post-hoc* and for correct trials only. Go RTs were calculated as the number of samples between the start and end of movement multiplied by the sample rate (1/60Hz). Velocity was calculated as the mean number of pixels moved in the Y-direction per sample. For signal trials, a pre-signal baseline measure of velocity was taken as the mean velocity across samples from the start of motion (excluding the first 3 samples) until the sample where the signal was presented (established *post-hoc* as the first sample where the Y<SOD[110]). Signals were marked incorrect if this pre-signal baseline was compromised by any of the reasons indicated for incorrect go trials (occurring prior to signal presentation). Pre-signal velocity was calculated as the mean velocity across these samples. This provided a baseline for measurement of slowing and stopping of responses after signal presentation.

[110] Where SODs corresponded to 20%, 40% and 60% of the distance between the start and target locations- Y-axis co-ordinates: 566, 434 and 303, where Y=0 at the top of the screen.

Post-signal slowing and stopping of cursor movement was measured for all signal trials. Slowing was defined as the reduction in post-signal velocity to 30% (or less) of the pre-signal velocity, and stopping defined as the absence of change velocity over successive samples. The point of change on change trials was identified as the point in which the X-coordinates were found to move towards the change location. In the continuous task, the point of slowing, stopping or change was identified as the first of three successive samples where these criteria were met, whereas this only had to occur on one sample in the discrete task[111]. However, it should also be noted that in the change condition, one sample instances of slowing or stopping were recorded between the signal onset and the point of change. This was to establish whether action updating could be measured in the absence of response slowing or stopping. One sample was used as the duration of slowing/stopping prior to a change was not known. Stop and change trials were marked as correct if the stop or change occurred prior to the cursor reaching the target and the pre-signal baseline was not compromised.

Signal RTs were estimated as the number of samples between the presentation of the signal and the point of slowing, stopping or change (separately) multiplied by the sample rate. Updating distances were also computed as the Euclidean distance (in pixels; as per Morein-Zamir & Meiran, 2003) between the cursor position at signal onset and the point of slowing, stopping or change (separately). Euclidean distance was used here to account for variations in natural mouse movement across participants and computed as:

$$Euclidean\ Distance = \sqrt{((X_2 - X_1)^2 + (Y_2 - Y_1)^2)}$$

where X_1 and Y_1 correspond to the X- and Y-coordinates of the mouse position at the point of signal onset and X_2 and Y_1 correspond to the X- and Y-coordinates of the mouse position at the point of slowing, stopping or change. Analyses were conducted over all stop and change signals separately and were also separated according to SOD for further analysis.

[111] Although there is potential for task differences between the continuous and discrete versions of the task, the additional samples to meet the slow/stop/change requirement on continuous trials was necessary due to the identification of one- and two-sample instances of slowing/stopping/change during piloting, with the absence of additional updating evidence in the continuous task (e.g. velocity was increased or X-coordinates moved in the opposite direction due to natural movements). In the discrete task any change in the velocity or direction of the cursor is indicative of release of key or execution of an additional response, respectively. Only marginal differences were established when two- or three- sample criteria were used.

7.3.4.2. Stop-signal task analysis

SST data were analysed in accord with previous chapters (Section 2.3.1; although note only the integration method was used to estimate SSRTs). Incorrect go trials were considered those where participants responded to the incorrect direction of the arrow and omissions. Stop signal trials were incorrect if any response was made. GoRTs were computed as the time between stimulus onset and response execution.

7.3.4.3. Self-report analysis

Average measures of self-report task-related difficulty and frustration were converted into percentages for each condition and participant separately as per Study 3 (Sections 6.3.2.1.4 and 6.3.2.2).

7.3.4.4. Test-retest reliability and variability

Test-retest reliability describes the consistency in measures obtained across different time points and situations, while variability can be used to describe the distribution of data around the mean (Shrout & Fleiss, 1979; Vaz, Falkmer, Passmore *et al.*, 2013). Both are important considerations when designing paradigms/measures for psychological phenomena to ensure replicability of effects (Vaz *et al.*, 2013). Here, *within-session* measures of test-retest reliability and variability were computed for the tasks within the current study and SSRTs acquired from studies 1-3[112]. The methods used to compute intraclass correlation coefficients (ICCs) and coefficients of variability (CV) are outlined in APP10.3.6.4.

[112] For studies 1-3, SSRTs were estimated separately for each behavioural run and averaged across the first and second halves of each study to provide two separate estimates per participant for comparison. For study 2, SSRTs were explored for the sham condition only. N=30 for all experiments. For the current study, relevant measures of action updating were computed separately for the first 4 blocks and second 4 blocks of each task for comparison. Notes regarding participant exclusions for the current study are noted in the results.

7.4. Results

The results primarily describe action updating with respect to the stop/change task, with a focus on error likelihood and the potential relationships between inhibitory and non-inhibitory action updating measures. Results for the standard SST and relationships with inhibitory measures obtained from the stop/change tasks are reported. Finally, test-retest reliability and variability of measures between tasks are compared. Note that one participant failed to complete the second behavioural run of the discrete stop task and the second behavioural run of the standard SST and was therefore excluded from the test-retest reliability and variability analyses.

7.4.1. Error likelihood in the stop/change task

Error likelihood was explored using error rates. To ascertain whether error likelihood was matched across stop and change conditions both subjective and objective measures were explored. Analysis of self-report ratings of task-related difficulty and frustration revealed no differences between the stop and change conditions in the continuous ($t_{(23)}$=-0.21, p=.838, BF=0.22; $t_{(23)}$=0.82, p=.421, BF=0.29, respectively) or discrete ($t_{(23)}$=0.03, p=.976, BF=0.22; $t_{(23)}$=-0.55, p=.59, BF=0.25, respectively) versions of the stop/change task. However, while stop and change error rates were comparable in the continuous task[113] (M=40.23%, SD=24.86% and M=42.4%, SD=27.15%, *respectively*; $t_{(23)}$=-.8, p=.434, BF=0.29), participants were more successful at stopping ongoing responses than executing an alternative response (M=35.94%, SD=18.61% and M=44.66%, SD=21.33%, respectively; $t_{(23)}$=-5.9, $p_{.025}$<.001, BF=3987.17) in the discrete task. This could simply be an artefact associated with the execution of the additional response or early release of the key on stop signal trials as the cursor approaches the target.

To establish whether successful action-updating potential between stop and change conditions was the result of signal onset distance (SOD) a series of repeated measures ANOVAs were conducted. SOD (SOD1, SOD2, SOD3, which refer to signal onsets 20%, 40% and 60% of the total distance between the start and target locations, respectively) and updating condition (stop and change) were entered as factors and

[113] Note, that stop signal accuracy measured via a reduction of velocity to 30% of the pre-signal velocity yielded exactly the same results as accuracy measured via the outright stopping (and 0 velocity) of movement across both continuous and discrete tasks.

percent error as the DV (all results are illustrated in Figure 7.8). In the continuous task, a significant main effect of SOD was revealed ($F_{(1.21,27.93)}$=57.68, p<.001, Greenhouse-Geisser corrected, BF=1.35^{e+20}), but no main effect of updating condition ($F_{(1,23)}$=0.53, p=.474, BF=0.2) or interaction between SOD and updating condition was found ($F_{(2,46)}$=0.92, p=.407, BF=0.16). Increased SOD was related to increased error likelihood in both the stop and change conditions (SOD3>SOD2>SOD1, all p<.001, all BF>292.9).

Conversely, in the discrete task, a significant main effect of SOD ($F_{(2,46)}$=101.4, $p_{.05}$<.001, BF= 1.79^{e+35}), updating condition ($F_{(1,23)}$=33.57, $p_{.05}$<.001, BF=0.42) and interaction between SOD and updating condition ($F_{(2,46)}$=4.57, $p_{.05}$=.015, BF=0.31) were detected. As in the continuous task, increasing SOD in the discrete task was found to be related to increased error likelihood (SOD3>SOD2>SOD1, all p<.001, all BF>63.77). The main effect of condition was driven by greater error likelihood on change relative to stop signal trials. Simple main effects analysis established a disparity in accuracy between stop and change error rates at SOD3 only (SOD3: $t_{(23)}$=6.69, $p_{.0167}$<.001, BF= 39219.87; SOD1: $t_{(23)}$=1.57, p=.131, BF=0.63; SOD2: $t_{(23)}$=1.96, $p_{.}$=.062, BF= 1.2).

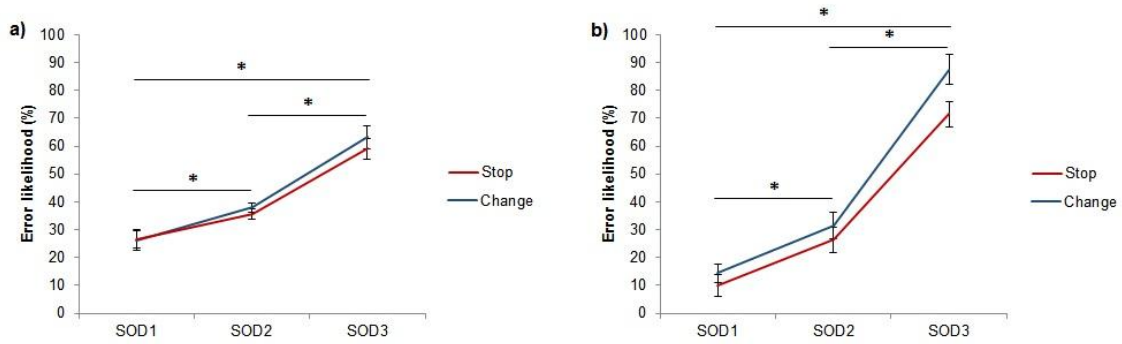


Figure 7.8. Error rates rates across stop (red) and change (blue) signals for **(a)** continuous and **(b)** discrete tasks over signal onset distances (SOD), where SOD 1 is closest to the start location and SOD 3 closest to the target location. ***** =significant difference after comparison to Holm-Bonferroni adjusted α. Error bars= ±1 within subject standard error (Cousineau, 2005; Morey, 2008).

Error rates were greater for discrete go trials presented in the stop relative to change conditions (11.65% compared to 7.81%; $t_{(23)}$=3.57, $p_{.025}$=.002, BF=22.76), and the majority were the result of participants' stopping the cursor movement prior to reaching the target (stop condition: M=7.25, SD=5.57% vs. change condition: M=4.69,

SD=4.52%; $t_{(23)}$=4.01, $p_{.05}$=.001, BF=59.45). To explore the potential for proactive slowing in the continuous task (where participants had ample opportunity to adjust the speed of responding to maximise performance)[114], mean velocity on go trials were explored. Mean velocity was found to be slower (less Y-pixels travelled per sample) when continuous go trials were presented alone (i.e. without any possibility of a signal appearing) than when they were presented in the stop and change tasks ($F_{(1.26, 28.85)}$=13.81, $p_{.05}$<.001, Greenhouse-Geisser corrected, BF=910.11; stop> go: $p_{.017}$<.001, BF=237.3; change>go: $p_{.025}$=.003, BF=13.17). This difference is likely due to practice effects as go trials were only presented at the beginning of the experiment. However, no overall difference in mean velocity was identified between continuous go trials presented in the stop and change conditions ($p_{.05}$=.261, BF=0.39; see Figure 7.9a). Although this does not discount the potential for strategic responding, this indicates that the strategies adopted may be comparable across stop and change conditions. This is supported by similar go-response accuracy across the continuous stop and change conditions ($t_{(23)}$=0.13, p=.899, BF=0.22).

Further analyses were conducted to investigate whether there were differences in response strategies on go trials in the stop and change continuous task conditions, which may not be observed when the mean velocity across the whole trial is analysed together, As such, I explored the available distance was divided into thirds to provide an indication of mean velocity (and potential differences between the tasks) at the beginning, middle and end of each go trial. Repeated measures ANOVA with point of trial (beginning, middle, end) and condition (stop, change) as factors with mean go velocity as the DV revealed a significant main effect of the point of trial ($F_{(1.56,35.89)}$=97.54, $p_{.05}$<.001, Greenhouse-Geisser corrected, BF=6.56^{e+32}). Velocity was found to be greatest at the middle of movement, as opposed to the beginning ($p_{.017}$<.001, BF=3.36^{e+8}) or end of movement ($p_{.025}$<.001, BF=3.1^{e+7}). This is likely due to the physical constraints on mouse movement within the available response space (i.e. acceleration is necessary to start moving the cursor, and deceleration is likely associated with the full extension of the arm upon reaching the target). No significant difference between the velocity at the beginning and end of movement was found ($p_{.05}$=.054, BF=1.23; although note this may be due to the removal of initial samples from all responses). As illustrated in Figure 7.9b, this difference across time points is

[114] In the discrete task, velocity was fixed across all conditions within-participants and therefore proactive slowing was not possible.

demonstrated as an acceleration of movement from the beginning to the middle of the trial, with a subsequent deceleration of movement from the middle to the end of the trial. No main effect of condition was found ($F_{(1,23)}$=2.71, $p_{.05}$=.114, BF=0.24). However, an interaction between point of trial and condition was found ($F_{(2,46)}$= 13.37, $p_{.05}$<.001, BF=2.66) and qualified by increased velocity on go trials when presented in stop relative to change conditions at the beginning ($t_{(23)}$=2.64, $p_{.0167}$=.015, BF=3.51) and middle ($t_{(23)}$=2.57, $p_{.025}$=.017, BF=3.1) of movement, but not at the end of movement ($t_{(23)}$=0.71, p=.487, BF=0.27). Although this may indicate potential proactive slowing of responses at early stages of movement in change conditions relative to stop conditions, the difference is very small (Figure 7.9b).

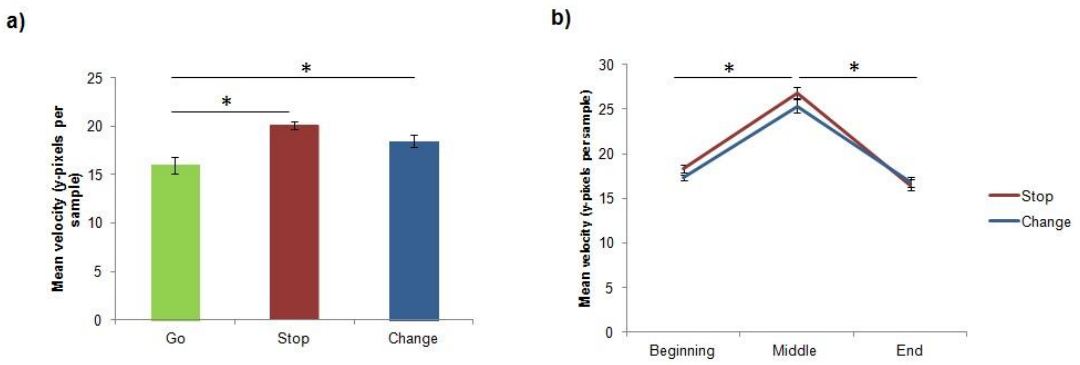


Figure 7.9. (a) The mean velocity on continuous go trials when presented alone (green), within the stop condition (red) or within the change condition (blue). **(b)** The mean acceleration and declaration in velocity over the course of a trial when the available distance for movement was divided into three. Beginning, middle and end describe the beginning, middle and end of movement, for stop (red) and change (blue) conditions. Velocity was computed as the change in Y-pixels per sample. ***** =significant difference after comparison to Holm-Bonferroni adjusted α. Error bars= ±1 within subject standard error (Cousineau, 2005; Morey, 2008).

The velocity prior to signal onset (rather than the division of the available movement space) also demonstrated velocity to be increased on stop relative to change conditions. Repeated measures ANOVA with pre-signal velocity as the DV and SOD (SOD1, SOD2, SOD3) and condition (stop, change) as factors established that pre-signal velocity increased with increasing SOD ($F_{(1.07,24.56)}$=216.86, $p_{.05}$<.001, Greenhouse-Geisser corrected, BF=3.26^{e+31}; where SOD3>SOD2>1, all p<.001, all BF>8.4^{e+9}). Velocity was found to be greater on signal trials in the stop relative to change conditions ($F_{(1,23)}$=7.82, $p_{.05}$=.010, BF=1.81). No interaction between SOD and

condition was found ($F_{(2,46)}$=1.59, p=.216, BF=0.15), indicating the difference between stop and change pre-signal velocity was consistent across signal onsets (Figure 7.10).

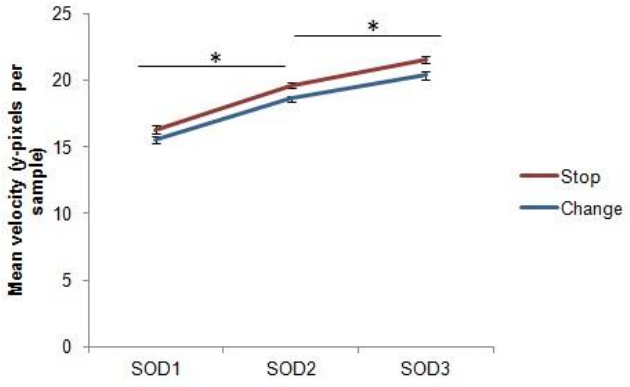


Figure 7.10. The change in pre-signal velocity across signal onset distance (SOD; where SOD 1 is closest to the start location and SOD 3 closest to the target location) in the continuous stop (red) and change (blue) tasks. ***** =significant difference after comparison to Holm-Bonferroni adjusted α. Error bars= ±1 within subject standard error (Cousineau, 2005; Morey, 2008).

Linear regression analyses revealed go-velocity within each task to be a good predictor of signal accuracy across the conditions (continuous stop: $F_{(1,22)}$=49.205, p<.001, R^2=0.69; continuous change: $F_{(1,22)}$=33.4, p<.001, R^2=0.78; discrete stop: $F_{(1,22)}$=65.94, p<.001, R^2=0.74; discrete change: $F_{(1,22)}$= 53.41, p<.001, R^2=0.71), and accuracy was found to decrease by 2.19-4.45% per pixel increase in velocity on average (Figure 7.11). Importantly, this highlights the possibility that the task may not be adequate to fully appreciate the action updating abilities of particularly fast responders. Indeed, the fastest responder was found to successfully inhibit only 3.13% of stop trials and successfully adjust response trajectory on 5.21% change trials. For this participant, continuous go-velocity was on average 41.94 pixels per sample, more than double the mean go-velocity of the remaining participants (M=18.42, SD=5.06 pixels per sample). This poor performance is likely associated with the limited available space for responding and the presumably extended duration required to update an on-going action plan at high speed.

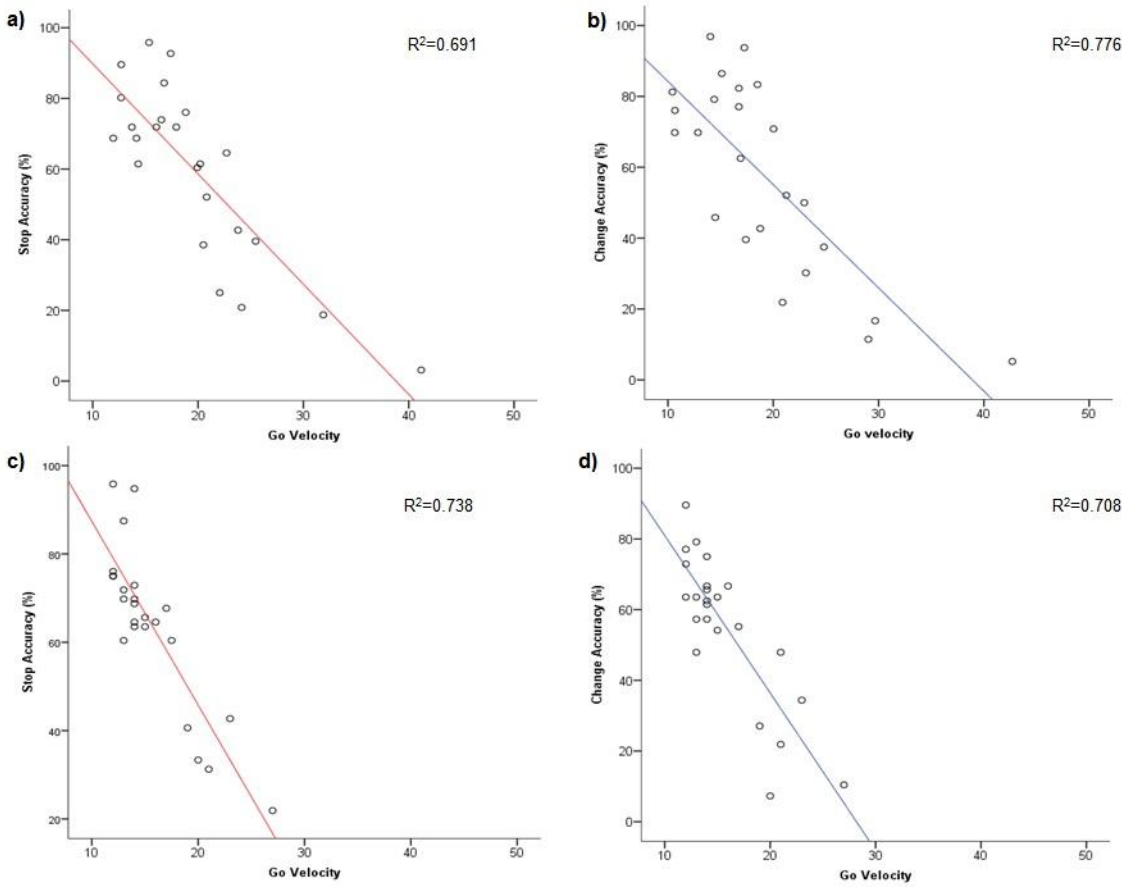


Figure 7.11. Summary of linear regressions computed to assess how well mean go velocity was able to predict accuracy on each task. **(a)** Continuous stop accuracy was found to decrease by 3.12% per pixel increase in velocity; **(b)** continuous change accuracy was found to decrease by 2.19% per pixel increase in velocity; **(c)** discrete stop accuracy was found to decrease by 4.16% per pixel increase in velocity; **(d)** discrete change accuracy was found to decrease by 4.45% per pixel increase in velocity. Go velocity is calculated as the mean number of Y-pixels moved per sample and refers to the velocity on go trials within the corresponding conditions. R^2 values are reported for each linear fit.

7.4.2. Recruitment of inhibition in the change condition

An empirical question to be answered as part of this study was whether it is possible to change mouse trajectory without recruitment of inhibitory processes. Instances of slowing and stopping after signal presentation but prior to the point of successful change on continuous change signal trials were analysed. It should be noted that instances of slowing and stopping only had to occur on one sample before a successful change response (between the onset of the signal and the start of the response). As noted above, the duration of expected slowing or stopping before a change was unknown, and thus a conservative approach was adopted to establish whether action updating could be measured in the absence of response slowing or stopping. A reduction in velocity to 30% or less than the pre-signal velocity was considered slowing, a value selected *a priori*. However, post-hoc plots of % slowing of velocity after signal presentation and before a successful change response support this as a selected measure (Figure 7.12).

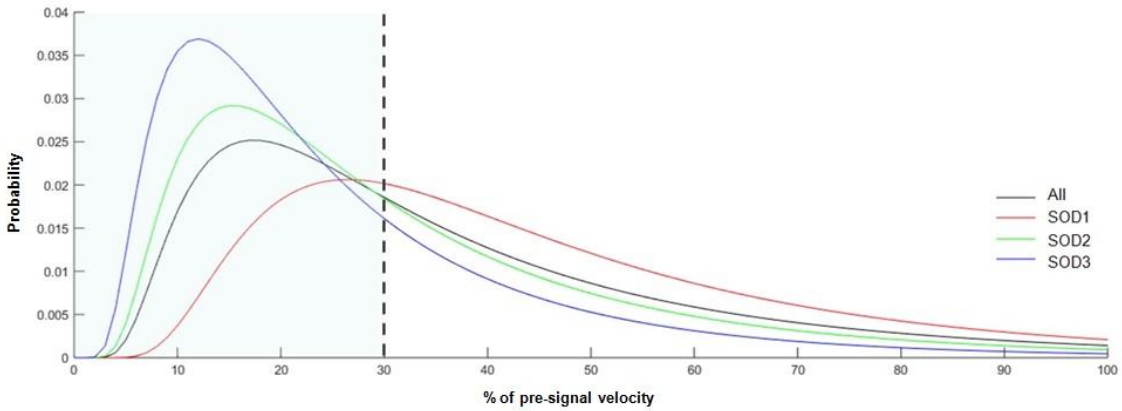


Figure 7.12. Representation of the amount of slowing prior to a successful change response in the continous change task. Here, post-signal slowing was considered the minimum velocity change between successive samples between the onset of the signal and the point of change, converted into a % based on pre-signal velocity. Distributions were fit using an inverse Gaussian kernel as slowing prior to change response was assumed to be non-normal. Distribution curves are shown for all change signals (black), and signals presented at different distances: closest to the start location (SOD1 = red), closest to the target location (SOD3 = blue) and the interim signal onset location (SOD2 = green). The shaded area represents trials that met the *a priori* criteria in which slowing was deemed a reduction in velocity to 30% (or less) of the corresponding pre-signal velocity. Data are representative of all instances of slowing (not outright stopping) on all successful change trials.

Incidence of slowing and stopping prior to a successful change response was found on 48.29% and 15.58% of change signal trials, respectively. Repeated measures

ANOVA revealed these instances to be increased as SOD increased ($F_{(2,46)}$=7.48, p=.002, BF=19.42; Figure 7.13), where instances of slowing and stopping where less so at SOD1 relative to SOD2 and SOD3 (both p<.001, BF>2.01^{e+6}), but there was no overall difference in instances between SOD2 and SOD3 (p=.661, BF=0.24). As expected slowing occurred more often than stopping ($F_{(1,23)}$=111.66, p<.001, BF=1386^{e+10}). There was an interaction effect established between slowing/stopping and SOD ($F_{(1.59,36.63)}$=4.91, p=.019, Greenhouse-Geisser corrected, BF=1.19), where slowing was found to occur significantly more often than stopping across all SODs (all p<.001, BF>292.6).

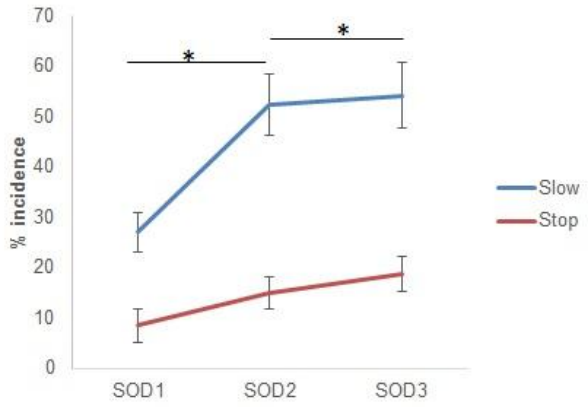


Figure 7.13. % incidence of slowing (blue) and stopping (red) prior to successful change responses in the continuous change task across different signal onset distances (SOD), where SOD 1 is closest to the start location and SOD 3 closest to the target location. ***** =significant difference after comparison to Holm-Bonferroni adjusted α. Error bars= ±1 within subject standard error (Cousineau, 2005; Morey, 2008).

7.4.3. Relationships between stop/change measures

Here, I tested whether updating measures (i.e. RTs and distances) were supported by the same constructs. Within task-type (i.e. continuous or discrete) correlations were established between stop and change RTs (Table 7.1) and distances (Table 7.2). Positive correlations indicate that the different types of updating measured here may be mediated by some of the same mechanisms.

Table 7.1. Correlations of time to update within the different action updating tasks.

Task	Measures	r	*p*	α	BF
Continuous	Slow vs. stop	**0.58**	.003	.0167	**13.73**
	Slow vs. change	0.35	.094		0.8
	Stop vs. change	**0.59**	.002	.0125	**16.46**
Discrete	Stop vs. change	**0.51**	.010	.025	**4.54**

Note. **Task** refers to whether the correlations were computed for dependent measures within either the continuous or discrete tasks; **Measures**- whether instances of slowing, stopping or change were analysed; **r=**Pearson's correlation coefficient, significant r values are reported in bold; ***p***=p-value; **α**=alpha level for comparison after Holm-Bonferonni correction; **BF**= Bayes Factor, BFs>3 are reported in bold. Correlations were not computed separately for the reaction time to slow in the discrete condition as these values were identical to the time to stop. All degrees of freedom=22.

Table 7.2. Correlations of distance to update within the different action updating tasks.

Task	Measures	r	*p*	α	BF
Continuous	Slow vs. stop	**0.997**	<.001	.0125	**2.86^{e+22}**
	Slow vs. change	**0.68**	<.001	.05	**117.84**
	Stop vs. change	**0.69**	<.001	.025	**153.48**
Discrete	Stop vs. change	**0.94**	<.001	.0167	**8.99^{e+8}**

Note. **Task** refers to whether the correlations were computed for dependent measures within either the continuous or discrete tasks; **Measures**- whether instances of slowing, stopping or change were analysed; **r=**Pearson's correlation coefficient, significant r-values are reported in bold; ***p***=p-value; **α**=alpha level for comparison after Holm-Bonferonni correction; **BF**= Bayes Factor, BFs>3 are reported in bold. Correlations were not computed separately for the distance to slow in the discrete condition as these values were identical to the distance to stop. All degrees of freedom=22.

The relationships between slow, stop and change RTs and distances (analysed separately) within both the continuous and discrete tasks were moderated/mediated by mean go-velocity (added as a covariate). Table 7.3 shows the significance status of the *p*-value for the original correlations has either reduced to below .05 (evidence of a mediating influence of mean go velocity) or to below the original *p*-value but above .05 (evidence of a moderating influence of mean go velocity). Such results, although not surprising, indicate that the speed of responding has an obvious influence on the time and distance to update a response.

Table 7.3. Summary of the moderating/mediating influence of mean go reaction time on the relationship between action updating measures.

Measure	Task	Conditions	r	*p*	original *p*
Reaction time	Continuous	Slow vs. stop	0.31	.154	.003
		Stop vs. change	0.41	.051	.002
	Discrete	Stop vs. change	0.2	.366	.010
Distance	Continuous	Slow vs. stop	0.99	<.001^{+}	<.001
		Stop vs. change	0.48	.019	<.001
		Stop vs. change	0.49	.019	<.001
	Discrete	Stop vs. change	0.86	<.001^{+}	<.001

Note. **Task** refers to whether the correlations were computed for dependent measures within either the continuous or discrete tasks; **r**=Pearson's correlation coefficient, ***p***=p-value. Note that only relationships that were originally found to be correlated were including in these moderating/mediating analyses in accord with the recommendations of Baron & Kenny, (1986; see also Judd, Kenny, & McClelland, 2001). All degrees of freedom=21. $^{+}$*p*-values have reduced but only marginally, original and adjusted *p*-values <1^{e-5}. Mediating effects are highlighted in orange and moderating effects are highlighted in blue.

I also assessed whether there were relationships between the time and distance to either stop or change responses across different effectors (i.e. across the continuous and discrete tasks; Table 7.4). While there appeared to be no or inconclusive relationships between RTs to stop and change signals, there did appear to be significant correlations between the distance to stop and change subsequent to the onset of a signal.

Table 7.4. Correlations between reaction time to slow, stop and change across the continuous and discrete tasks. Correlations between distances to slow, stop and change across the continuous and discrete tasks

Measure	Conditions	r	*p*	α	BF
Reaction time	Slow cont vs. Stop disc	0.15	.472		0.27
	Stop cont vs. Stop disc	0.33	.119		0.69
	Change Cont vs. Chang disc	0.33	.116		0.69
Distance	Slow cont vs. Stop disc	**0.6**	<.001	.0167	**19.85**
	Stop cont vs. Stop disc	**0.61**	.002	.025	**24.12**
	Change Cont vs. Chang disc	**0.49**	.017	.05	**3.46**

Note. **Task** refers to whether the correlations were computed for dependent measures within either the continuous or discrete tasks; **r**=Pearson's correlation coefficient; significant r-values are reported n bold; ***p***=p-value; **α**=alpha level for comparison after Holm-Bonferonni correction; **BF**= Bayes Factor, BFs>3 are reported in bold; **Cont=** continuous; **Disc=** discrete. Correlations were not computed separately for the distance to slow in the discrete condition as these values were identical to the distance to stop. All degrees of freedom=22.

7.4.4. Action updating across distance

As accuracy and mean velocity were found to be dependent on SOD, I further explored how RTs and distances may also change with SOD. Figure 7.14 illustrates that as SOD increases, updating RTs and distances decrease. This is to be expected as at longer distances, updating needs to occur quickly otherwise the response would be incorrect. Separate repeated measures ANOVA were conducted to explore the relationships between updating RTs and distances, with SOD and condition. In the continuous tasks, updating RTs were found to be influenced by SOD ($F_{(1.15,24.2)}$=115.83, $p_{.05}$<.001, Greenhouse-Geisser corrected, BF=4.33^{e+14}) and condition ($F_{(1.1,23.03)}$=30.16, $p_{.05}$<.001, BF=6.66^{e+10}), although no interaction between these factors was found ($F_{(1.46,30.61)}$=1.68, p=.207, BF=0.09). RTs were found to consistently decrease across conditions with increasing SOD (all p<.001, all BF>1.91^{e+6}). Stop RTs (in the stop condition only) were found to be consistently greater than slow RTs ($p_{.017}$<.001, BF=8.15^{e+13}) and change RTs ($p_{.025}$<.001, BF=3025.14). This is not unexpected given that slowing would necessarily occur prior to outright stopping and slowing itself is more common prior to a successful change response that stopping itself (Figure 7.13). No difference between the slow and change RTs were observed (p=.849 BF=0.23), which may be due to the large number of instances in which slowing occurred prior to change responses (Figure 7.14).

In the discrete condition, RTs were also found to be influenced by SOD ($F_{(1.06,19.14)}$=20.91, $p_{.05}$<.001, Greenhouse-Geisser corrected, BF=974.18), driven by a decrease in updating RTs with increased SOD (all $p_{.0167}$<.001, all BF>8.66). Contrary to the continuous task, here a main effect of condition ($F_{(1,18)}$=37.9, $p_{.05}$<.001, BF=896534.22) was found to be the result of increased change relative to stop RTs; a pattern found to be consistent across SODs due to the lack of interaction between SOD and condition ($F_{(1.03,18.56)}$=2.25, p=.150, Greenhouse-Geisser corrected, BF=0.64) and likely explained by the temporal difference in stopping a key press vs. stopping and then executing an additional key press.

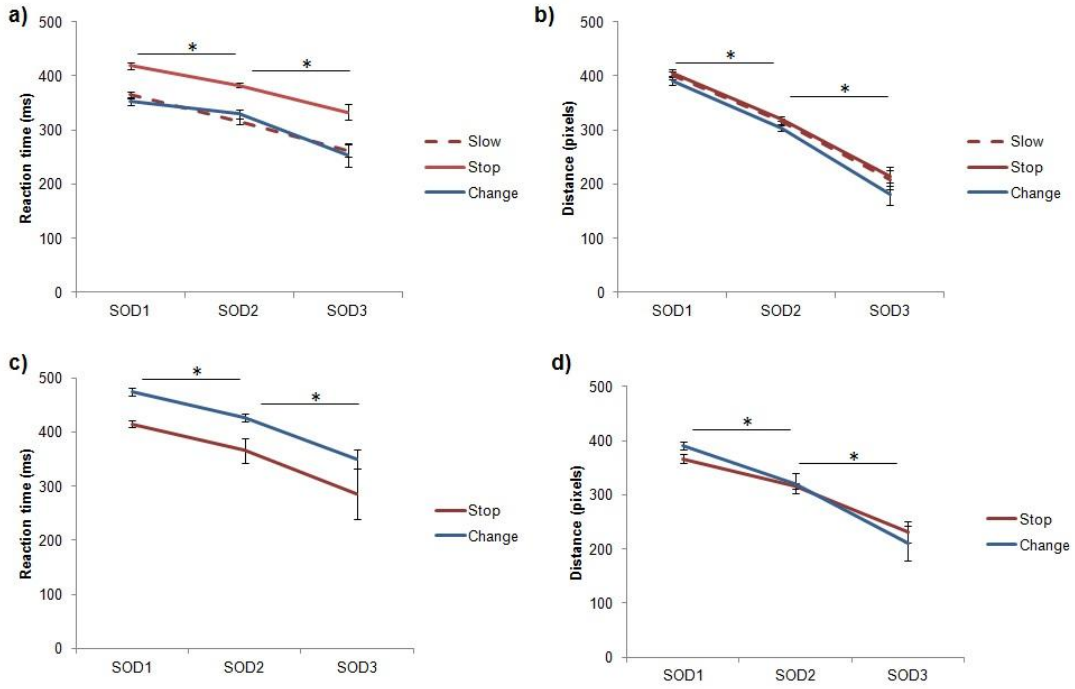


Figure 7.14. Changes in dependent measures with signal onset distance (SOD), where SOD 1 is closest to the start location and SOD 3 closest to the target location. **(a)** Illustrates the slow (red dashed), stop (red) and change (blue) RTs in the continuous task; **(b)** illustrates the Euclidean distance between signal onset and the position of slowing, stopping and change in the continuous task; **(c)** illustrates the stop and change response times in the discrete task; **(d)** illustrates the Euclidean distance between signal onset and the position of stopping and change in the discrete task. ***** =significant difference after comparison to Holm-Bonferroni adjusted α. Error bars= ±1 within subject standard error (Cousineau, 2005; Morey, 2008).

Distances were also found to vary across SODs and condition. In the continuous task, shorter updating distances were found with longer SODs ($F_{(1.12,23.57)}$=205.08, $p_{.05}$<.001, Greenhouse-Geisser corrected, BF=1.04^{e+8}; SOD1>SOD2>, all p<.001, all BF>7.1^{e+8}), but were greater under conditions of stopping relative to slowing ($F_{(1.02,21.34)}$=9.49, $p_{.05}$=.005, BF=2.29^{e+8}; $p_{.0167}$<.001, BF=3.02) and changing ($p_{.025}$=.003, BF=8.25^{e+12}), and slowing relative to changing response trajectory ($p_{.05}$=.018, BF=2.59^{e+16}). These effects were consistent across SODs and no interaction between signal onset and distance was found ($F_{(1.72,36.15)}$=1.05, $p_{.05}$=.352, Greenhouse-Geisser corrected , BF=0.43).

In the discrete task, increased SODs also led to decreased updating distances $F_{(1.09,18.52)}$=52.3, p<.001, Greenhouse-Geisser corrected, BF=5.97^{e+13}; SOD1>SOD2>SOD3: all p<.001, all BF>4633), but were found to be greater in response to change as opposed to stop requirements ($F_{(1,17)}$=8.09, p=.011, BF=1.6),

consistent across SODs (no interaction effects were found: $F_{(1.03,17.44)}$=0.3, $p_{.05}$=.599, Greenhouse-Geisser corrected, BF=0.18). Outlier removal did lead to a significant interaction effect between task and SOD ($F_{(1.35,17.6)}$=10.59, p=.002, BF=0.7) and change distances were found to greater than stop across all SODs (all p<.032, all BF>2959; see APP10.6.4.3.4).

Together the ANOVA results reveal that the distance between the start of motion and signal onset has a significant influence on the ultimate time and distance of implementation of updating requirements. The closer the signal onset was to the target (and therefore further from the start position), the shorter the updating distances and RTs. This opposes what we might anticipate given that mean pre-signal velocity increases with SOD; in that it might be expected that the faster one moves the harder it is to update and so more time and distance is required to be successful. However, in accord with the assumptions of the independent horse race model, successful inhibition will only occur in circumstances where the stop process is fast enough to win the race against the go process (Logan & Cowan, 1984). This may extend more broadly to general action updating processes.

7.4.5. Comparison with the stop-signal task

To corroborate the measures of response inhibition as measured in the novel stop/change paradigm, relationships with measures associated with the classic SST were explored. Initial investigation of SSRTs yielded from the standard SST indicated substantial slowing of responses for three participants, indexed by negative SSRTs. These datasets were excluded from further analysis. The remaining 21 participants performed in line with expectations, with high go-trial accuracy (M=97.72%, SD=2.39%) and successful inhibition occurring on ~50% of stop signal trials (M=49.95%, SD=3.25%) demonstrating the efficacy of the dynamic tracking method used to set SSDs. Although overall mean RTs for go trials (M=453.9ms, SD=51.84ms) were found to be longer than mean RTs on unsuccessful stop trials (M=446.9ms, SD=46.81ms) this difference was not reliable ($t_{(20)}$=0.92, p=.367, BF=0.33). Exploration of the percentile distributions of go RTs and RTs to unsuccessful stop signals confirmed instances in which go RTs were shorter than unsuccessful stop RTs at the 50th and 60th percentiles (Figure 7.15). The subtraction of mean successful goRTs from unsuccessful stop RTs across individuals demonstrates this to be the case for 38% (8/21) of

participants. The reasons for such a large number of deviations from expected performance are unclear; however participants were reimbursed with course credit as opposed to cash payment and did not have as much training on the SST as in previous studies reported in this thesis. Thus motivation and practice are likely key factors. Additionally, although the dynamic tracking method appeared to yield performance in accord with expectations (i.e. successful inhibition occurred on ~50% stop signal trials) participants may have adopted different response strategies to those employed in previous tasks (where there were 6 SSDs and therefore less likely to be able to predict signal onsets). Verbruggen & Logan (2015) recommend excluding participants for whose SSRTs are unreliably estimated. As such, the following analyses were conducted exclusive of these datasets (although I acknowledge the likelihood of imprecision of findings given the small sample). For completion, correlations inclusive of these datasets are reported in APP10.6.4.4.

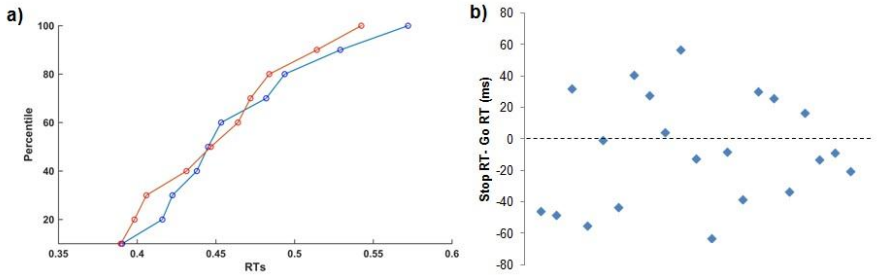


Figure 7.15. (a) the distribution of unsuccessful stop RTs (red) and go RTs (blue) in the current stop signal task. Interactions between stop and go RTs are evident at the 50th and 60th percentiles; **(b)** illustrates the distribution of difference scores computed by subtracting RTs to go trials in the SST from RTs corresponding to unsuccessful stop signal trials for the current SST.

Correlational analyses of SSRT with RTs and distances to slow and stop in the discrete task were not found to be related (Table 7.5). Similarly, there was no correlation found between go RT in the SST and go RT in the continuous task ($r_{(11)}$=0.34, *p*=.255, BF=0.56) or go RT in the SST and go RT in the discrete task ($r_{(11)}$=0.021, *p*=.946, BF=0.35). These results indicate the potential for different mediating mechanisms underlying stop performance in the SST and continuous and discrete stop/change tasks.

Table 7.5. Summary of correlations between SSRT with distances to slow and stop on stop signal trials in the continuous and discrete tasks.

	Continuous				Discrete	
	Slow RT	Stop RT	Slow Dist	Stop Dist	Stop RT	Stop Dist
SSRT	0.14	0.07	-0.29	-0.3	0.06	-0.39
BF	0.31	0.28	0.43	0.44	0.28	0.62

Note. **SSRT**=stop signal reaction time in the standard SST as estimated using the integration method; **RT**= reaction time; **Dist**=distance, **BF=**Bayes Factor. Values correspond to Pearson's correlation coefficients. α-level not reported as all *p*-values>0.05. All degrees of freedom=11.

7.4.6. Test-retest reliability and variability

ICCs, SEMs and CVs (both within and between participants) are presented in Table 7.6. ICCs can range from 0 to 1, where an ICC of 0 suggests complete absence of reliability, and an ICC of 1 suggests complete reliability. Large ICCs are typically associated with low measurement error and high between–subject variability (Shrout & Fleiss, 1979), and low-within subject variability is key to ensuring low measurement error. Although there is no consensus at to the qualitative boundaries of ICCs, it has been suggested that ICCs above .6 are of use (Chinn, 1991). Our data suggest that the SSRTs (from the SST) as measured for the current study is below this acceptable standard (ICCs=0.29 - 0.39), whereas SSRTs from studies 1-3 are both below and above this level (ICCs=0.48-0.75). However, *within-session* test-retest reliability for the RTs and distances acquired via the stop/change tasks fare far better with ICCs above .6 and some above .8 (ICCs=0.63-0.93), which is considered a marker of excellent reliability (Cicchetti & Sparrow, 1981; Landis & Koch, 1977).

The low test-retest reliability obtained for SSRTs in the current study appear to be the result of large SEMs (54.28ms-67.99ms) and large CV_{wp} (28.18%-40.21%). Whilst greater between subject-variability was found (29.37%-35.53%), the large measurement error and within subject variance negate these advantages. Additionally, the small sample sizes used in these tasks (due to a large number of exclusions) is likely to render the means, upon which the CV computations are based, unreliable. The highest test-retest reliability obtained were associated with the discrete stop/change task. Here, the low measurement error and small within-participant variability is likely the result of the restriction of parameters (including direction of cursor movement and

velocity) and the simplicty of task performance, relative to the alternative paradigms. Between-subject variability appeared within the range of those produced by other variables (11.65%-15.75%, compared with 11.8% and 17.26% for the continuous stop/change task and 13.62% and 17.75% for the SSTs reported in studies 1-3).

Comparison of the SSTs used in studies 1-3 and the continuous stop/change task reveal greater test-retest reliability for the latter. Even though CV_{bp} were comparable, SEM and CV_{wp} for the SSRTs in the stop/change task (21.5ms-27.31ms) were generally smaller than those associated with the standard SST (20.99ms-31.55ms).

Table 7.6. Summary of the test-retest reliability and coefficients of variation computed for stop and change reaction times and distances across Studies 1-4.

Study #	Relevant chapter	DV	ICCs	SEM	CVwp	CVbp
Study 1	2	Mean SSRT	0.49	31.55	12.08	16.21
		Integ SSRT	0.55	23.64	8.28	13.62
Study 2	4	Integ SSRT	0.61	25.5	8.99	14.32
Study 3	6	Integ SSRT	0.75	20.99	8.27	17.75
Study 4	7	Integ SSRT	0.29	67.99	40.2	35.53
		Integ SSRT*	0.39	54.28	28.18	29.37
		cSLRT	0.71	29.88	6.32	14.89
		cSLDIS	0.84	20.87	5.2	14.84
		cSSRT	0.63	27.31	5.51	11.8
		cSLRT	0.71	29.88	6.32	14.89
		cSLDIS	0.84	20.87	5.2	14.84
		cSSRT	0.63	27.31	5.51	11.8
		cSSDIS	0.83	20.97	5.17	14.82
		cCHRT	0.65	37.25	9.2	17.26
		cCHDIS	0.7	29.42	6.53	15.44
		dSSRT	0.79	21.5	3.41	11.74
		dSSDIS	0.83	35.49	3.84	15.75
		dCHRT	0.9	16.84	2.85	11.65
		dCHDIS	0.93	15.63	3.65	15.52

Note. **ICC**=intracclass correlations; **SEM**= standard error of measurement; **CV_{bp}**=coefficient of variation between participants; **CV_{wp}**= coefficient of variation within participants; **SSRT**=stop signal reaction time; **SSDIS**=stop signal distance; **CHRT**=change RT; **CHDIS**=change distance; **SLSRT**= slow RT; **SLDIST**= slow distance; **c**= measure was acquired from the continuous task; **d**= measure was acquired from the discrete task. The method used to estimate SSRT is prefixed by either **Mean** (to indicate the use of the mean method) or **Integ** (to indicate the use of

the integration method). For all experiments, measures were averaged across the first half of each study and the second half of each study for comparison. Studies 1-3, N=30. Study 4, N=21 and * indicates N=13. ICCs are represented as a ratio between 0 and 1, SEM in the corresponding unit measurement (ms for reaction time and pixels for distance) and CVs in %. Corresponding studies and relevant chapters are noted.

7.5. Discussion

The aim of the current study was to develop a novel paradigm that could be used to provide analogous measures of inhibitory and non-inhibitory action updating, whilst minimising the error likelihood and response conflict differences between tasks. This paradigm also enabled the direct measurement of action updating, thus circumventing drawbacks associated with estimation of stop latencies based on the independence assumptions underlying the independent horse-race model (Logan & Cowan, 1984; Bissett & Logan, 2014; Verbruggen & Logan, 2015). Furthermore, the continuous version of the stop/change task overcomes issues of temporal differences in updating responses in the presence of a signal across stop and control conditions (as was the case in the context-cueing paradigm). Greater test-retest reliability and smaller measurement error was also identified in the stop/change task. I argue that the continuous stop/change task may therefore provide a reliable alternative to more classically applied stop-signal paradigms.

The stop/change task provides many advantages over the context-cueing paradigm, with the most prominent being the matching of error-likelihoods across different action updating conditions. In both the continuous and discrete versions of the task, subjective ratings of task-related difficulty and frustration were comparable. This was mirrored in the continuous task, where performance was found to be similar across updating conditions. Moreover, increased error likelihood with increasing SOD was also found in both stop and change tasks. This is reminiscent of the standard SST, in which the probability of successful inhibition is reduced by increased delay between stimulus and signals onsets (Logan & Cowan, 1984). A discrepancy in the pattern of accuracy measures was found in the discrete paradigms, where stop and change accuracy diverged at the SOD closest to the target. Stop signal performance was found to be better than change performance at this SOD only, and is likely associated with the requirement to stop and then execute an additional response in the change task.

Continuous mean go velocity (indicative of Y-distance covered per sample) was found to be greater at the beginning and middle of the trial in the stop condition relative to the change condition. Consistent with this, mean pre-signal velocity on signal trials was also greater on continuous stop trials relative to continuous change trials. Although this may be reflective of a proactive slowing strategy to confer greater change success, the difference was found to be very small. Overall mean go velocity over the entire expanse of the trial did not differ between stop and change tasks. Additionally, such slowing is not as problematic as observed in the standard SST, where proactive slowing can have a direct effect on SSRT (as demonstrated here by the exclusion of participants due to the presence of negative SSRTs).

A question posed in this study was whether it was possible to establish action updating measures in the absence of recruitment of inhibitory processes. That is, whether change responses were possible without stopping in the continuous change task. My findings suggest that this *may* be possible under certain situations, such as when the SOD is short (this is discussed in more detail below). Outright stopping of movement prior to successful continuous change responses was rare (occurring on 15.58% of all successful change responses), but slowing preceded almost half of successful change trials (occurring on 48.29% of all successful change responses). It is possible that this may indicate the recruitment of a braking system that is partially implemented when mouse trajectory is changed or when a salient signal is detected (Wessel & Aron, 2013; Aron *et al.*, 2014a). In accord, RTs for outright stopping in the continuous stop/change task were longer than RTs to change a response, suggesting a difference in the degree to which a braking system may be implemented across the trial types.

Increased SOD was found to be associated with increased slowing/stopping of responses prior to a successful change response. Given that participants were required to change the mouse trajectory from moving towards an upper left or right target to the centre of the screen, this is likely due to the increased angle at which the mouse was required to move in order to make a successful change. However, this interpretation does not explain why accuracy in the discrete change task also reduces, and is associated with more errors than the stop task, with increased SOD. It is probable that as participants approach the target location, they prepare to stop their response and thus stop success is more likely. The preparation to stop responses is also evident in the deceleration of continuous go velocity (in both stop and change conditions) as the

mouse approaches the target. Also possible is the potential for a more abrupt implementation of updating processes when there is limited time/distance and decreased updating success likelihood (as accuracy was also found to decrease with increasing SOD). This interpretation also explains why RTs and distances to update decrease with increasing SOD. Future work should aim to explore inhibitory and non-inhibitory action updating at shorter SODs to prevent recruitment of alternative, potentially opposing, processes that are likely to confound the measure of interest.

In both the continuous and discrete stop/change tasks, updating RTs and distances were not found to correlate. This finding contradicts that of Morein-Zamir & Meiran (2003) who established a high positive correlation between SSRT and stop signal distance in their mouse-tracking paradigm. This, they argue, demonstrated that stopping comprised the resulting stopping distance, even though these measures were dissociable in their sensitivity to task variables. Paradoxically, in the current study, such correlations were not found. The reason for this is unclear, but is potentially driven by the small sample size, and comparable between subject variability in these measures for which correlational relationships are dependent (Tabachnick & Fidell, 2007; Field, 2013).

Within the continuous and discrete tasks, RTs and distances between conditions were found to correlate (e.g. stop RT and change RT) and were found to be moderated/mediated by the difference in go-response velocity between updating conditions. Consequently, while the relationship between action updating measures was in part due to speed of mouse movement this was not the only underlying construct. This indicates that although similar accuracy, RT and distance patterns were found between stop and change conditions across SODs, the measures were not the result of the implementation of exactly the same action updating process. The mediating relationship between velocity and action-updating processes in both stop and change tasks may be evident in the slowing of movement prior to updating. Significantly, such observations are consistent with findings in the discrete stop/change literature where the stop/change task has been conceptualised as an extension of the standard SST, not the result of different processes *per se* (see Boecker, *et al.,* 2013 for a review). This may be further indicative of the potential to update responses in the absence of response inhibition under some circumstances. However, it is also important to note that the moderating influence of go-velocity suggests a degree of dependency between go and

action-updating processes[115]. This is problematic for estimations of SSRT in the standard SST but has no consequences for the direct measurement of stop/change latencies. This is particularly advantageous given the go/stop dependency identified in the SST employed in the current study and that found in previous work (e.g. Bissett & Logan, 2014; Ozyurt *et al*., 2003; Verbruggen & Logan, 2015).

Exploration of the relationship between go and stop RTs in this thesis established dependency between stop and go processes in even the simplest SSTs. Verbruggen & Logan (2015) suggested that such dependence occurs mostly under particularly demanding situations, such as when stopping rules are frequently changed. Although it could be argued that the rule-switching between blocks in the context-cueing paradigm could increase demands on the rule-based system, the most common violations were identified in the current study where the task remained consistent[116]. Here, in addition to overlapping RT distributions between stop and go RTs, a third of participants demonstrated mean signal-respond RTs longer than mean go RTs. This undermines the predictions of the independent race model which assumes that unsuccessful stop RTs should be consistently shorter than go RTs because the failure to stop is due to the go process finishing earlier than the stop process (Logan & Cowan, 1984). The violation of the assumptions of the independent race model render SSRTs unreliable and as such corresponding participants were excluded from the analyses (Verbruggen & Logan, 2015). The continuous stop/change task is therefore more economical given the non-reliance on models to estimate the latencies of the action updating processes. The extent of violations identified here may also explain the lack of relationships identified between indices of response inhibition between the stop/change task and the SST.

Although the continuous stop/change task offers many advantages, further task validation is required. The greater test-retest reliability of the stop/change tasks relative to the SST would need to be fully examined. Measurements need to be acquired on different days and separated by different time-frames to avoid confounding practice and fatigue-related confounds and over-estimation (Chinn, 1991; Vaz *et al.*, 2013). It is also important to establish whether the continuous stop/change task is susceptible to the same variables as the standard SST (as per Morein-Zamir's tests involving stimulus-

[115] Although note dependency between go and stop processes in continuous tasks have not been identified previously (Logan & Cowan, 1984; Logan, 1994; Morein-Zamir *et al.*, 2004).
[116] Although speculatively switching between different tasks may have contributed additional (and unexpected) demands.

response compatibility, signal probability and signal modality; Morein-Zamir & Meiran, 2003; Morein-Zamir *et al.*, 2004, 2006) and whether impairments in inhibitory performance is found in patient groups (as per Morein-Zamir *et al.*, 2008; Scheres *et al.*, 2003, 2004).

In addition, a number of modifications to the design of this study could improve its efficacy in future research. The use of a computer mouse is familiar for most participants, but its use with the current design could prove problematic with certain populations. For example, patients with movement limitations may find whole arm extension (as required in this task) difficult[117]. Conversely, groups familiar with speeded mouse movements (e.g. gamers), may find the distance available too limited for us to fully appreciate their action updating abilities. Indeed, as identified here, the fastest responder in the continuous stop/change task was also found to produce the most errors. To circumvent these issues tasks involving smaller, continual movements could be used. Care would need to be taken to avoid confounding of measures with additional measures, such as consistent and more variable velocity adjustments found in scribbling tasks (Sosnik *et al.*, 2007), for example.

Nevertheless, even in its current state, the data from this study indicate the continuous stop/change task to be favourable over the standard SST for the reasons discussed. Importantly, the design of the stop/change task allows us to better control for non-inhibitory confounds than was possible in the context-cueing paradigm, although a degree of inhibition does appear to be recruited in the change task. Aron *et al.* (Wessel & Aron, 2013, Aron *et al., 2*014) would argue that this is indicative of the recruitment of inhibition (a partial 'brake') upon presentation of salient stimuli. However, if this was the case, then slowing would be expected to occur on *all* signal trials. Error likelihood and subjective ratings of task difficulty and frustration are matched and proactive response strategies appear limited and do not influence dependent measures to the same extent as in the SST. Future research can also take advantage of opportunities the continuous task affords that are not addressed here. These include the exploration of trial-by-trial variability in action updating strategies and responses, and the possibility to obtain more fine grained detail in decision making tasks through exploration of mouse trajectories.

[117] Though the use of a mouse could prove useful to some patient groups (e.g. those with Parkinson's disease) who find fast, discrete responding (as required in the SST, for example) difficult.

Chapter 8 General discussion

Although classic notions of executive control have considered response inhibition a unique function (e.g. Miyake *et al., 2*000), recent frameworks have replaced the inhibitory 'homunculus' with a simple set of processes that contribute to action-related decisions (Stuss & Alexander, 2007; Verbruggen *et al., 2*014). Such models are in-keeping with the recognition that the term inhibition is a global concept and that many different processes contribute to the ability to countermand ongoing actions. While studies have begun to explicitly control for the role of ancillary processes in response inhibition research (Chatham *et al.,* 2012; Dodds *et al., 2*011; Erika-Florence *et al., 2*014; Hampshire, 2015; Tabu *et al., 2*011), addressing this issue was the primary motivation for the work presented in this thesis. This chapter provides an overall summary and synthesis of the principal findings. This discussion is divided according to questions that I aimed to answer: (1) Is there evidence of a unique prefrontal system associated with the requirement to inhibit a response? (2) How does the rIFG support action updating? (3) Are subcortical structures recruited differently under conditions of response execution and response inhibition? (4) Can we improve measures of inhibitory and non-inhibitory action updating? Methodological limitations and future research directions are also considered.

8.1. Summary and discussion of findings

8.1.1. Is there evidence of a unique prefrontal system associated with the requirement to inhibit a response?

Whether sub-regions of the prefrontal cortex uniquely act to implement response inhibition is contentious (cf. Aron *et al., 2*014a, 2014b, 2015; Hampshire & Sharp, 2015a, 2015b). While some argue a specific neural module housed within either the rIFG or pre-SMA exerts inhibitory control (e.g. Aron *et al., 2*003, 2007; Aron & Poldrack, 2006; Li *et al., 2*006; Floden & Stuss, 2006; Nachev *et al., 2*007; Picton *et al., 2*006), others posit that response inhibition is merely the product of a series of broader cognitive processes (Erika-Florence *et al.,* 2014; Hampshire & Sharp, 2015a, 2015b; Hampshire, 2015; see also conceptual frameworks of Stuss & Alexander, 2007 and

Verbruggen *et al.*, *2*014). The primary pre-registered aim of Study 1 (Chapter 2) was to establish the neuroanatomical distribution associated with inhibitory and non-inhibitory action updating, to test whether a unique prefrontal network supports response inhibition that is dissociable from that supporting non-inhibitory action updating.

The combination of a modified version of Verbruggen *et al.*'s (2010) context-cueing paradigm and fMRI revealed widespread fronto-parietal activity commonly recruited under both inhibitory and non-inhibitory action updating conditions. Consistent with studies employing the SST and DT, overlapping activity was identified in the pre-SMA and the posterior rIFG, the *pars opercularis* (Chatham *et al.*, 2012; Erika-Florence *et al.*, 2014; Hampshire, 2015; see also Dodds *et al.*, *2*011). While these studies conclude that there is no evidence for a specialised inhibitory node within the *pars opercularis* (as implicated by Aron *et al.*, *2*014a, 2014b, 2015), further investigation suggests otherwise. It appears that the use of a spatial smoothing kernel in Study 1 may have distorted the pattern of activity in the rIFG with that of surrounding regions, and may have given a false impression as to the extent of rIFG recruitment under different action updating conditions. Unique recruitment of the *pars opercularis* under conditions of response inhibition increased from 12.7% with the application of a spatial smoothing kernel to 41.2% without (see Figure 5.1 and 5.2 and Tables 2.2 and 5.1). Furthermore, the specific coordinates of the unique inhibitory module provided by Aron *et al.* (2014b, MNI=48, 16, 18; see also Levy & Wagner, 2011) were activated under SST relative to DT conditions in Study 2, but under both conditions in Study 1. Contrasting the patterns of BOLD activity acquired in Study 1 with that in Study 2 demonstrates how the smoothing kernel spatially blurs activity, which appears more pronounced in the anterior direction (Figure 5.1 and 5.2). Thus it is possible that the use of spatial smoothing kernels in previous work (Chatham *et al.*, *2*012: 5mm FWHM; Dodds *et al.*, *2*011: 6mm FWHM; Erika-Florence *et al.*, *2*014: 8mm FWHM; Hampshire *et al.*, *2*010, 2015: 8mm FWHM) and in Study 1 (5mm FWHM), might have led to erroneous conclusions. To confirm this conjecture, raw data would need to be subjected to re-analysis with and without a spatial smoothing kernel[118].

It should be noted that the entirety of the *pars opercularis* was not recruited specifically under conditions of response inhibition; the posterior portion was activated

[118] This emphasises the importance of data archiving in fMRI (Poldrack & Gorgolewski, 2014) as the data would be readily available for re-analysis. As mentioned in Chapter 1, I also plan to archive my (anonymised) data within my thesis that appear in peer reviewed literature.

under both inhibitory and non-inhibitory action updating requirements. Speculatively, this might indicate a sub-division within the *pars opercularis* that reconciles findings of previous work. The posterior *pars opercularis* might support action updating more generally (in accord with Verbruggen *et al., 2*010; Chatham *et al.,* 2012; Erika-Florence *et al.,* 2014; Hampshire & Sharp, 2015a; Hampshire, 2015; Dodds *et al., 2*011; Levy & Wagner, 2011), while the anterior *pars opercularis* may support response inhibition specifically. Response inhibition was also found to exclusively recruit activity in the anterior rIFG, the *pars triangularis* (Study 1: 69.32%, Study 2: 17.93%), a region proposed to support responding with uncertainty (Levy & Wagner, 2011). The recruitment of the *pars triangularis* in the SST may have arisen as a result of conflicting task instructions (be fast, but stop where possible). While it is possible this region might also be exclusively associated with the requirement to stop a response (and exacerbated by the smoothing kernel), no such specificity has been identified in imaging studies employing similar tasks (Chatham et al., 2012; Dodds *et al.,* 2011; Erika-Florence *et al.*, 2014; Hampshire & Sharp, 2015a; Tabu, *et al.*, 2011).

As discussed in Chapter 2 (Section 2.5), these incongruities are likely due to differences in the way in which the tasks were implemented. In studies that employ both SST and DT (e.g. Chatham et al., 2012; Erika-Florence *et al., 2*014; Hampshire *et al., 2*010; Hampshire, 2015a), signal presentation is more infrequent than my own (33% of trials here, relative to Chatham *et al., 2*012: 25%; Hampshire *et al., 2*010: 26%; Hampshire *et al., 2*015: 25%; Erika-Florence *et al., 2*014: 26%), and tasks were only presented once, as opposed to in an interleaved manner as in the context-cueing paradigm. It is possible that these differences led to increased response control demands in previous work relative to my own induced by less probable signals and reduced learning opportunities over time. Furthermore, Chatham *et al.* (2012) always presented the DT before the SST[119] which may have led to differences in response control requirements relating to task novelty and the acquisition of new rules, potentially increasing the control demands of their DT relative to the DT employed in Studies 1 and 2. Additional monitoring and working memory demands are likely in other tasks, such

[119] The authors note that this was to prevent the signal being associated with stopping in the DT, to ensure effortful cancellation of actions in the SST (as participants would have already associated the signal with double-responding).

as the *complex* task employed by Erika-Florence *et al.* (2014) and Hampshire (2015; Figure 1.12)[120].

If the rIFG activity established in Studies 1 and 2 is the result of different response control demands (including error detection and conflict resolution), then this region may not house a specific module for implementing response inhibition and may instead be part of a broader network supporting multiple cognitive processes (see Hampshire & Sharp, 2015a for a review).

In Chapter 6, I consider evidence from Studies 1 and 2 that suggest the SST is associated with greater response control requirements than the DT. Evidence includes the greater error-likelihood, response conflict and ACC and DLPFC recruitment associated with the SST relative to the DT. Speculatively, the delay between stimulus and signal onsets in the context-cueing paradigm might have also contributed as they were optimised for the SST rather than the DT. This could have introduced greater response conflict and ambiguity in the SST relative to the DT. In Study 3 I explored the task demands associated with the SST and DT, using both psycho-physiological and self-report measures. The use of visual analogue scales (VAS) was anticipated to detect subtleties in how difficult and frustrating participants found the tasks comprising the context-cueing paradigm (see also Li *et al., 2*006, 2008; Spunt *et al., 2*012). Self-report measures indicate the SST was more difficult and frustrating than the DT and ignore task (IT). Indirectly, this suggests that the differences in rIFG activity observed in Studies 1 and 2 may have been due to increased SST-related demands relative to the DT. However, to enable concrete inferences, subjective reports require investigation in direct relation to %BOLD in the rIFG. Indeed previous work has found a relationship between self-report frustration in the SST and %BOLD in the ACC (Spunt *et al., 2*012)[121].

The potential for the pattern of activity to be associated with additional response control demands as opposed to the inhibition of a response inhibition specifically is in-keeping with Verbruggen *et al.*'s (2014a) conceptual framework of action control. As

[120] In the *complex* task, participants monitored the presence of frequent left and right pointing arrows and responded only on presentation of a signal (an arrow pointing up or down). However, the required responses differed depending on which way the infrequent arrow was facing. A single response was required upon presentation of an upward facing arrow, but a double response on downward facing arrows.
[121] Li *et al.*,(2006, 2008) observed no reliable relationship between SST-related frustration and %BOLD in either superior frontal or precentral regions, but these studies were likely confounded by their use of extreme descriptors (see limitations Section 8.2.5).

outlined in Chapter 1, Verbruggen *et al.* propose that, at a basic level, all actions are the product of 3 distinct processes: (1) signal detection, (2) action selection, and (3) action execution (Figure 8.1). Under this framework, response inhibition is conceptually similar to other forms of response control, with the decision to stop considered a form of response selection (see also Logan, *et al.*, 2014; Mostofsky & Simmonds, 2008; Rubia *et al.*, 2001). Thus it is possible that the overlapping activity observed in Studies 1 and 2 may be representative of neural networks that support the basic processes underlying action control.

But how would Verbruggen *et al.*'s model account for the additional and unique activity observed under conditions of response inhibition relative to non-inhibitory action updating? According to Verbruggen *et al.* additional ancillary processes (outlined in Figure 8.1) contribute to each stage of action control as a means to bias competing representations to produce the most appropriate output. In the SST, the conflict induced by the competing stop and go processes likely increases the recruitment of additional functions as a means to resolve this competition. Such recruitment is likely further increased as a means to successfully arbitrate between the speed and accuracy instructions in the SST (i.e. to respond as fast as possible, but stop upon presentation of a signal). In Figure 8.1 I have summarised how the ancillary processes identified by Verbruggen *et al.* might have been observed under SST conditions in Studies 1 and 2. Briefly, increased ACC activity under SST conditions is likely to be associated with the increased error likelihood and performance monitoring required in the SST (e.g. Botvinick, *et al.*, 2001), particularly when decision making is difficult (Forstmann *et al.*, 2012; Keuken *et al.*, 2015). Proactive response strategies are also adopted to improve successful inhibitory performance (Verbruggen & Logan, 2008; Verbruggen & Logan, 2009c; Aron, 2011). Furthermore, the DLPFC is likely recruited under conditions where task rules and representations require updating (Barber *et al.* 2013; Brass *et al.*, 2005; Bunge, Kahn, Wallis *et al.*, 2003; Crone *et al.*, 2006), and may work with the ACC as a means to implement successful performance monitoring (e.g. Botvinick, *et al.*, 2001). While this evidence indicates that ancillary processes might indeed contribute to successful SST performance, it is unclear whether the unique rIFG activation observed is also result of the increased adoption of such processes. Greater control over non-inhibitory processes in response inhibition research is required in future work.

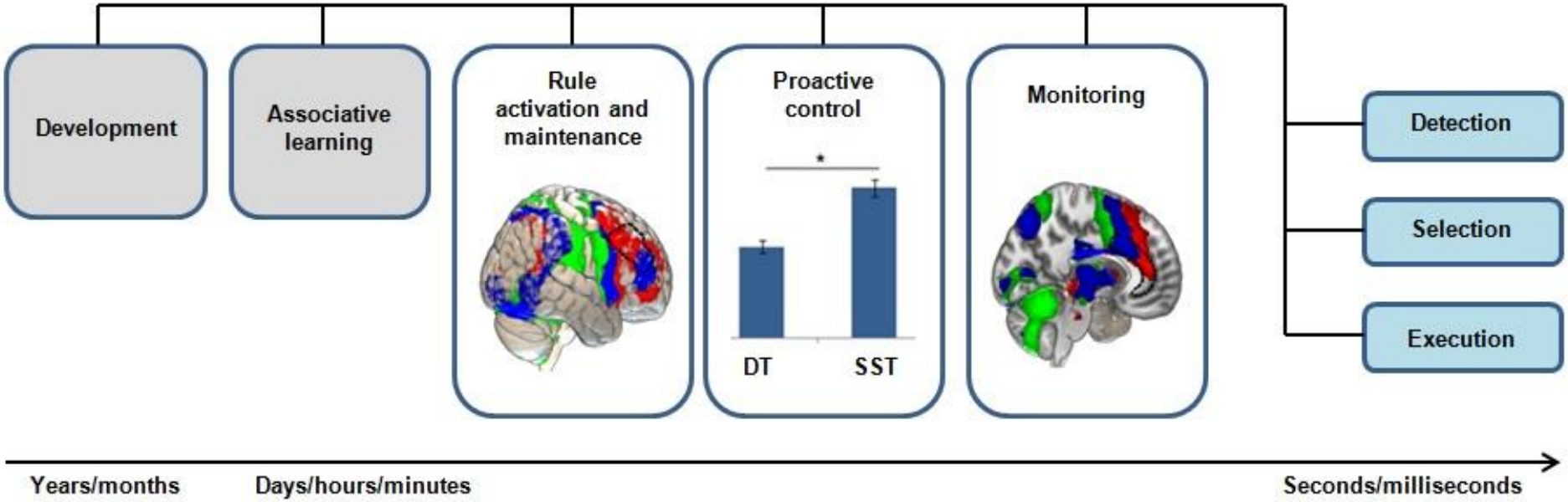


Figure 8.1. Under Verbruggen *et al.*'s (2014) conceptual framework all forms of action control are the product of signal detection, response selection and response execution, and each of these stages can be influenced by additional processes. These processes include monitoring, proactive control, rule activation and maintenance, associative learning and development. Here, I highlight the processes that might recruited to a greater degree in the SST relative to the DT and thus contribute to the differential pattern of activity established. Increased proactive control requirements are evidenced by the increase in RT to no-signal trials in the SST relative to the DT. Increased DLPFC and ACC activity in the SST (red), relative to the DT (green) is likely the combined result of performance adjustments (monitoring, error detection and conflict resolution) and updating rules in working memory as means to arbitrate between the conflicting task instructions in the SST.

Aside from the rIFG, other frontal regions were also explored in Studies 1 and 2, including the pre-SMA, which has been implicated as crucial to the implementation of response inhibition (e.g. Floden and Stuss, 2006; Nachev *et al.*, 2007; Picton *et al.*, *2*006; Chen *et al.*, 2009; Cai *et al.*, 2012; Obeso *et al.*, *2*011). %BOLD change in the pre-SMA under conditions of inhibitory and non-inhibitory action updating was not found to differ in either Study 1 or 2. However, it is noteworthy that there were differences in the spread of related activity within the vicinity of the pre-SMA. The requirement to stop a response was associated with an anterior spread of activity within the pre-SMA, connected to activity in the ACC and DLPFC. The requirement to add to a response was associated with a posterior spread of activity within the pre-SMA, connected to activity in the SMA. Given the evidence outlined in Chapter 1 (see Section 1.2.2.2), the divergence of this distribution likely relates to the additional demands associated with the SST (i.e. error and performance monitoring and therefore greater ACC and DLPFC; e.g. MacDonald, Cohen, Stenger & Carter, 2000; Sharp *et al.*, 2010; Brown & Braver, 2005) and with the DT (i.e. execution of an additional response and therefore greater SMA; see Nachev, Kennard & Husain, 2008 for a review).

Overall, while the pattern of rIFG activity established under different action updating conditions suggests a unique prefrontal system associated with the requirement to inhibit a response, this could reflect differences in response control demands associated with processes not controlled for in the context-cueing paradigm. It is therefore possible that response inhibition is the product of the combined effects of multiple cognitive processes (Verbruggen *et al.*, *2*014), which the rIFG (and pre-SMA) may support. However, whether or not the rIFG comprises part of a multiple demand cortex (Duncan & Owen, 2000, Duncan, 2001, 2010, 2013) as proposed by Hampshire *et al.* (2014, 2015, 2015b) requires further confirmation. Given the discussion of Verbruggen *et al.'s* model above it seems plausible, but the findings presented here highlight the need for such investigation with improved control over non-inhibitory processes that contribute to SST performance. Prospective work could also explore the effect that simple adjustment to task rules (and subsequent error-likelihood) has on the spread of activity within the rIFG and pre-SMA (e.g. see Badre & D'Esposito, 2009, Botvinick, 2008, and Duncan, 2013) which would better inform their role in supporting action control.

8.1.2. How does the rIFG support action updating?

Recent evidence has demonstrated the potential for a role of the principle inhibitory neurotransmitter GABA in supporting response inhibition and impulsivity (see Hayes *et al.*, 2014 for a review). The primary pre-registered aim of Study 2 was to establish whether there were any relationships between behavioural indices of action updating and GABA concentration within the rIFG. As relating behaviour to GABA has proven challenging (Puts & Edden, 2012), I attempted to introduce variability through use of an intervention. cTBS has been shown to elevate GABA levels in motor and occipital regions (Stagg *et al., 2*009; Allen *et al.,* 2014), while simultaneously reducing cortical excitability (Huang *et al., 2*005) and %BOLD (Hubl *et al., 2*008). When applied to the rIFG, cTBS has also been found to impair both inhibitory and non-inhibitory action updating performance (Verbruggen *et al., 2*010). If cTBS-induced modulations of measures were found to be related, then a link between behavioural, neurochemical and neurophysiological inhibition could be established. Contrary to expectations, cTBS was found to have no reliable effect on behavioural indices of action updating, GABA concentration or %BOLD (either within the rIFG or remote ROIs including the pre-SMA, BG and THAL). The lack of differences, confirmed by Bayesian hypothesis testing, may have been impeded by methodological limitations that should be considered in future work (see Section 8.2.3).

At baseline, however (i.e. after sham rather than active cTBS), there appeared to be potential for a correlational relationship between SSRT and GABA concentration within the rIFG, as well as GABA concentration and %BOLD within the rIFG (acquired from the contrast of (stop signal>stop no-signal)). Although inconclusive, negative correlations indicate that increased GABA is associated with more efficient inhibitory control and smaller %BOLD change. These results suggest that GABA-BOLD coupling within the rIFG may act to support response inhibition. If so, this relationship would extend previous work indicating that GABA supports motor plasticity and impulsivity (Bachtiar & Stagg, 2014; Blicher *et al.,* 2015; Paik & Yang, 2014; Floyer-Lea *et al.,* 2006; see also Hayes *et al., 2*014) and would further indicate a potential link between neurochemical and behavioural inhibition[122]. But how exactly would an inhibitory

[122] Previous research has shown increased BOLD activity in the rIFG to be associated with better inhibitory control (Aron & Poldrack, 2006). This relationship is contrary to what I propose here. As I found no evidence of correlations between SSRT and rIFG %BOLD in either Study 1or 2 (Tables 2.4 and 4.6), further work is needed to clarify the presence and direction of these relationships should they exist.

neurotransmitter in a frontal region be linked to behavioural inhibition implemented in the BG? Given that GABAergic neurons typically have short axons, they tend to exert their effects locally (Isaacson & Scanziani, 2011), and thus are unlikely to have a direct effect on BG activity[123]. Instead it is likely that GABA exerts its effects by influencing lateral inhibition (de la Vega, Brown, Snyder *et al.*, 2014). According to Hampshire *et al.* (2015a, 2015b), when participants anticipate the presence of a stop signal, activity in rIFG neurons is down-regulated. Upon presentation of a signal, these neurons become active, and motor slowing, and ultimately inhibition, is the result of lateral inhibition between competing representations. According to de la Vega *et al.*, (2014) increased GABA might result in the most active representation being inhibited quicker. If GABA exerts its effects by resolving the competition between different representations, then the rIFG may not support response inhibition *per se*, but rather supports the selection of one representation over another. Thus the faster selection between competing choices is likely realised in the SST because of the requirement to select between competing go and stop responses (as opposed to running an action plan to completion and selecting another as in the DT). Such biological potential is in-keeping with the potential role of the IFG in response selection and control demands (as discussed above) and with Verbruggen *et al*.'s (2014a) conceptual framework that argues that responses must be selected amongst competing options (see also Figure 8.1).

The use of Bayesian statistics was particularly informative in Study 2. Rather than rejecting H_1 in favour of H_0, the study provided insufficient evidence to substantiate either. This is of particular importance to the discussion of GABA-related findings above, but also in meeting the secondary aim of Study 2, to provide a part-replication of the cTBS-induced impairments in SSRT and DRT2 as established by Verbruggen *et al.* (2010). Contrary to my hypotheses, cTBS was not found to impair either inhibitory or non-inhibitory action updating performance. However, Bayesian meta-t-tests revealed evidence in favour of an effect of cTBS on SSRT (BF=2.36) and evidence in favour of no effect of cTBS on DRT2 (BF=0.51). Although more data are required to substantiate these results, they indicate the potential for the rIFG to specifically support response inhibition and not non-inhibitory action updating. As discussed in Section 8.1.1 there may well be evidence to support this specialisation, but

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It is possible %BOLD may have been reduced in Sudies 1 and 2 relative to previous literature, due to the extensive task training participants experienced.

[123] Furthermore, it is hypothesised that the BG are modulated by glutamatergic projections from the cortex (Albin *et al., 1*989; Alexander & Crutcher, 1990; Nambu *et al., 2*002; see Figure 1.15).

it is unclear due to methodological differences between studies. Furthermore, the rIFG may act to select between competing representations rather than implementing response inhibition specifically as noted above. If so, then how did cTBS to the rIFG impair DRT2 performance in Verbruggen et al.'s (2010) study? It has previously been suggested that this observation was the result of inadvertent stimulation of the posterior ventral premotor cortex (see Aron *et al., 2*014b, and Buch *et al., 2*010). However, this seems an unlikely explanation as such an impairment was not found in Study 2 and was not supported by the Bayesian meta-analysis. In-keeping with the possibility that rIFG activity is sensitive to response control demands as discussed above, it is possible that the context-cueing paradigm as employed by Verbruggen *et al.* (2010) was more 'demanding' that that used in Studies in 1 and 2. Specifically, in Verbruggen *et al.*'s version, the task context randomly switched every 4 trials (every 18 trials in Studies 1 and 2) and participants had to remember stimulus-response mappings across the sub-tasks as no task-cue was provided (I presented a cue informing participants of the task prior to each block). Thus response conflict and working memory demands are much greater in the context-cueing paradigm as employed by Verbruggen *et al.* (2010) relative to my own. Although I observed overlapping activity within the *pars opercularis* (the site of cTBS application in both Study 2 and in Verbruggen *et al., 2*010) it is possible that the impairments in DRT2 were not observed due to comparatively less demanding version of the context-cueing paradigm.

Additionally, the effects of cTBS on SSRT may not have been realised in Study 2 due to the context-cueing paradigm being complete in an MR as opposed to a lab environment (as used by Verbruggen *et al., 2*010). This is of particularly important when attempting to extrapolate findings from the lab to the MR, and vice-versa. Previous work has identified differences in RTs and accuracy rates between these locations (Koch *et al., 2*003; van Maanen *et al., 2*015; Hommel *et al., 2*012; Koten *et al., 2*013; Assecondi *et al., 2*010) and it is possible that the testing environment may have had a greater impact on behavioural performance than the intervention employed. This could be readily tested by repeating the study in either lab or scanner environments and comparing subsequent task performance.

Collectively, these results support the findings of the fMRI studies discussed in Section 8.1.1 and corroborate the possibility that the rIFG does house a specialised module crucial for the implementation of response inhibition. Speculatively, activity in this node may be supported by BOLD-GABA coupling. However, further investigation

is required: 1) to establish substantial evidence in favour of either H_1 or H_0 for these effects; and 2) to establish between alternative interpretations, including the role of the rIFG in increased response control demands (including conflict monitoring and error detection) and response selection.

8.1.3. Are subcortical structures recruited differently under conditions of response execution and response inhibition?

Response control is presumed to be implemented by top-down control mechanisms (Luria, 1966; Miyake *et al.*, 2000; Miller & Cohen, 2001), in which cortical structures are hypothesised to influence BG activity to facilitate or suppress motor output (Albin *et al.*, *1*989; Alexander & Crutcher, 1990; Nambu *et al.*, *2*002). Using the data acquired from Study 1 (Chapter 3), I conducted additional exploratory analyses to investigate whether the pattern of BOLD activity under conditions of response execution and response inhibition conformed to the putative direct, indirect and hyperdirect pathways (Albin *et al.*, *1*989; Alexander & Crutcher, 1990; Nambu *et al.*, *2*002). A novel compound contrast approach was employed to provide an average measure of activity under different response control conditions within each BG ROI. The pattern of data largely conformed to the expected activations and deactivations predicted by the pathways models- with activity under conditions of response execution consistent with the direct pathway and activity under conditions of response inhibition consistent with the indirect and hyperdirect pathways.

Exploration of patterns of data within left and right hemisphere ROIs revealed lateralised patterns of activity supporting different response control conditions. The requirement to inhibit a response was found to be supported by right-lateralised activity, while the requirement to execute a response was found to be supported by left-lateralised activity. Although potentially related to handedness (all participants responded with their right hands and were right-handed), these findings are consistent with models of motor control that argue for left hemisphere dominance in the acquisition of new motor skills and right hemisphere dominance in the amendment (in this case the inhibition) of ongoing action plans (Mutha *et al.*, *2*012).

Subsequent moderator/mediator analyses[124] were conducted to establish the interrelations amongst ROIs that were significantly activated under the different response control conditions. This approach is not as sophisticated as the modelling approaches employed elsewhere (e.g. Granger causality, psychophysical interactions, ancestral graphs and dynamic equation modelling; Duann *et al., 2*009; Jahfari *et al.,* 2011, 2012; Rae *et al., 2*015), but readily followed previous analyses (repeated measures ANOVA to determine the significance of activity within each ROI under each condition) and carries fewer assumptions than alternatives. The patterns of activity established between ROIs were consistent with previous work. Specifically, when responses were inhibited, the rIFG and right pre-SMA exerted mediating influence over BG structures (Duann *et al., 2*009; Jahfari *et al.,* 2011, 2012; Rae *et al., 2*015). The BG did not modulate activity in either cortical structure. This unidirectional effect is in accord with the dominant top-down model of response control (Luria, 1966; Miyake *et al.,* 2000; Miller & Cohen, 2001). A bidirectional relationship was found between the rIFG and right pre-SMA (although greater from the rIFG to the pre-SMA) as per previous findings (Jahfari *et al.,* 2011, 2012; Rae *et al., 2*015). The mediating relationships between ROIs were apparent in the downstream direction, in agreement with the relationships proposed by the pathways models (Albin *et al., 1*989; Alexander & Crutcher, 1990; Nambu *et al., 2*002; see also the hyper-indirect model proposed by Jahfari *et al., 2*011, 2012). However, strong interrelations between regions (both upstream and downstream) were evident under both response execution and response inhibition conditions. Such interrelations have not been identified in previous work. This is likely because more advanced effective connectivity analyses (for example the use of ancestral graphs by Jahfari *et al., 2*011, 2012) involve the selection of the model that best represents the pattern in the data. Conversely, the analytical approach adopted here explored the influence of all significantly activated ROIs upon one another, regardless of model fit. Although my method may not provide the most parsimonious model, it could prove complementary to more conventional approaches, enabling the identification of important relationships between ROIs as well as identifying which relationships are the strongest.

[124] In Frequentist statistics a covariate has a mediating influence on the relationship between two other variables if its incorporation eliminates the significance of the original relationship. If this significant relationship is reduced but not eliminated, the covariate can be described as having moderating influence on the original relationship.

Another important finding revealed by Study 1 (Chapter 3) is the role of the left GPe in response execution. The pattern of mediating effects suggests that the GPe acts as a 'transporter' of information received from the left STR to the left THAL. Although not conceived of in the original pathways models, it is recognised that the GPe may play a greater role in response control than originally anticipated (see Nambu, 2008). For example, recent work suggests the GPe is important for executing sequences of actions (Chan *et al., 2*006) as required in the DT. The role of the GPe in response inhibition is also worthy of further investigation in future work. In Study 1 it appears to exert a moderating influence over both cortical and subcortical structures, and in recent rat work, specific GABAergic projections from the GPe to the STR have been found to activated under stop relative to go conditions (Mallet *et al.,* 2016; although connectivity between the GPe and STR are recognised in the original pathways models; see Figure 1.15). Additionally, direct projections between the GP and frontal cortex (mediated by the STR; Milardi *et al.,* 2014; Chan *et al., 2*006; Saunders *et al.,* 2015) have also been identified, and indicate the potential for a fourth inhibitory pathway (Milardi *et al., 2*014). Thus, the dominant top-down model ascribed above and in previous work may not fully explain cortico-subcortical interactions in response control and further work is required to delineate the importance of these connections. Although it should be noted that the potential for a fourth inhibitory pathway projecting to the GPe was not realised in the pattern of activity established in Study 2. The right GPe was found to not exert mediating effects on other subcortical structures under conditions of response inhibition[125].

In Study 2 (Chapter 5), I attempted to replicate these findings. Although the lateralised activity under different response control conditions largely remained, the activity established in subcortical structures under conditions of response inhibtion were absent. Additional analyses revealed that this is probably due to the omission of the IT in Study 2. This likely decreased the effects originally uncovered under response inhibition conditions, and exacerbated the effects originally uncovered under response execution conditions. Under conditions of response execution, exclusion of the IT remarkably increased the spatial distribution of associated activity as well the number of interrelations between structures both within and between hemispheres. These findings highlight the necessity in selecting appropriate informative baselines in fMRI research

[125] The right GPe moderated relationships in other ROIs, but other ROIs exerted a mediating influence on the GPe, suggesting weaker functional efferents from the GPe relative to the functional afferents to the GPe.

(Mostofsky & Simmonds, 2008; Wiebking *et al.,* 2014) and are illustrative of a deeper problem for the interpretation of fMRI studies within this area- where the consideration of different tasks can have an enormous effect on the inferences that are made. This also highlights another benefit of pre-registration as it is clear that interpretations can readily differ depending on the contrast combinations employed.

Furthermore, Studies 1 and 2 also demonstrate the benefit of including both left and right ROIs in the analysis of subcortical activity in studies of response control. Imaging studies concerned with subcortical contributions to response inhibition typically interrogate a sub-set of right hemisphere ROIs (with the exception of the pre-SMA and STN which has been explored bilaterally; Rae *et al., 2*015; and the left caudate: Duann *et al., 2*009). The inclusion of both left and right BG structures provides an overview of the 'bigger picture' and could prove useful in exploring inter-hemisphere, as well as intra-hemisphere, relationships and provide future research opportunities. Moreover, as illustrated in the replication analyses in Study 2, this could help to establish the effects that slight task adjustment can have on resultant %BOLD patterns more widely.

Importantly, it is not clear how these results fit with models of action control that do not posit a specialised response inhibition network (e.g. Buss & Alexander, 2007; Verbruggen *et al.,* 2014a; see also Hampshire, 2015; Hampshire & Sharp, 2015a, 2015b). It is likely that differential patterns of neuronal responding in cortical sites activate distinct projections within the BG, but why would a network that supports broad processes become lateralised at the level of the subcortex? Potentially, the left and right BG may support cognitive processes beyond response execution and response inhibition, respectively. Such processes may not have been realised in the current work due to the exploration of limited forms of action control. However, the increase in interactions between left and right BG structures under conditions of response execution in Study 2, indicate that the lateralisation, while dominant, does not suggest exclusivity in BG structures recruited to support action control.

In summary, overall, my analyses support a distinction between a right-lateralised BG network of activity underlying the implementation of response inhibition, and a left-lateralised BG network of activity under conditions of response execution. While lateralisation has been indicated in previous work (e.g. Aron *et al., 2*003, 2007; Aron & Poldrack, 2006), left hemisphere BG ROIs have been largely neglected. Future

work could aim to explore the potential for the active 'blocking' of left hemisphere BG structures when a response is inhibited, as indicated (but not established) in Study 1. Furthermore, while conventional effective connectivity analyses enable the strongest patterns of activity amongst ROIs to be realised, the novel use of moderator/mediator analyses here enabled the exploration of interrelations between regions more generally, which could generate hypotheses for future research. The observation of top-down control could be further explored using concurrent TMS-fMRI, as pre-registered here: https://osf.io/89usr/. However, it also clear that contrasts used to uncover BG activity need to be carefully considered to ensure adequate baseline options are available. This will help ensure the stability of inferences. If used in future studies, the approaches here require improvement (with respect to establishing appropriate baselines) and replication. As noted above, this work would also benefit from improved control over non-inhibitory processes.

8.1.4. Can we improve measures of inhibitory and non-inhibitory action updating?

Throughout this thesis I have employed a modified version of Verbruggen *et al.*'s (2010) context-cueing paradigm. This combined task allowed action updating to be explored in both the presence (SST) and absence (DT) of inhibition (as well as with no updating requirements in the IT). The inclusion of the DT is justified as it provides a way of exploring action updating as a means to achieve goal-directed behaviour (in this case adding to an action plan), but in the absence of any obvious requirement to inhibit a response (Verbruggen *et al., 2*010; Dodds *et al., 2*011; Tabu *et al., 2*011; Chatham *et al., 2*012; Erika-Florence *et al., 2*014; Hampshire, 2015). However, as identified in Study 3 (Chapter 6), the inclusion of the DT does not control adequately for processes associated with error-likelihood and response conflict, which are greater in the SST relative to the DT. Additionally, the DT itself is confounded by the requirement to execute an additional response (Aron *et al., 2*014), although this is an inevitable design feature to ensure the final stages of the SST and DT are different.

In Study 4 (Chapter 7) I propose a continuous stop/change task, designed to provide analogous measures of inhibitory and non-inhibitory action updating. The study also aimed to assess whether the use of a continuous change task was a better control

for non-inhibitory processes than was possible using the DT, and fundamentally whether it was possible to measure action updating in the absence of inhibition. In this task participants are required to move a cursor towards a target, but on presentation of a signal either stop moving the cursor, or move the cursor towards an alternative location (depending on the block). The latency of the stop and change processes were computed as the time between signal onset and the time at which a successful stop or change occurred.

Participants performed comparably across the stop and change tasks, with similar accuracy rates overall as well as across individual signal onset distances (SODs). Additionally, there appeared to be no difference between subjective measures of task-related difficulty and frustration between the continuous stop and continuous change conditions. Furthermore, in the SST, proactive slowing is a strategy often adopted by participants to enhance their stop signal success (Aron & Verbruggen, 2008; Verbruggen & Logan, 2009c; Aron, 2011; see also Braver, 2012), but no such slowing was detected in the continuous stop task, and only to a limited degree in the change task. These advantages are of benefit to the wider literature and likely confer greater control over non-inhibitory processes than was possible in the context-cueing paradigm.

An empirical question posed by Study 4 was whether it was possible to measure action updating in the change condition without the requirement to slow or stop responses. This is an important question as discrete stop/change tasks and switch tasks often require a participant to stop one response in favour of another and consequently confounds such measures with inhibitory processes. In the continuous change task, I found that change responses were possible without corresponding slowing/stopping *some* of the time. Incidents of outright stopping before a successful change were minimal (15.6%), although there were more incidents of slowing (a reduction in velocity to 30% or less that observed prior to the signal) before a successful change (48.3%). These incidents were greater at longer SODs and are likely associated with the limited distance between signal onset and target position to smoothly change cursor trajectory without outright stopping. The absence of slowing on all signal trials counters the possibility that the presentation of a salient signal always recruits partial 'braking' (Aron *et al., 2*013, 2014a), and indicates that inhibition can be dissociated from other forms of action updating. This could be further informed by the use of modified versions of such tasks could be used in imaging environments to establish whether

similar neural correlates underlie performance in the continuous change when no slowing/stopping is evident and performance in the continuous stop task.

Another crucial benefit of the continuous stop task is in its ability to provide a direct measure of the latency of the stop process. In the SST, SSRT is estimated using the independent race model, which assumes independence between stop and go processes (Logan & Cowan, 1984). However, violations of these assumptions were detected in my own work (Chapter 7[126]) and that of others (Bissett & Logan, 2014; Verbruggen & Logan, 2015), rendering the corresponding SSRTs unreliable. The ability to directly measure the latency of the stop process is of benefit to the wider literature by circumventing the reliance on mathematical models to estimate SSRT. Additionally, the ability to acquire trial-specific measures of response inhibition enables the exploration of trial-by-trial variability in action updating performance (as per Morein-Zamir *et al.*, *2*008).

However, it must be acknowledged that the continuous stop/change task requires further validation. Test re-test reliability, although much better than in the standard SST, requires investigation over longer temporal delays than within a session as explored in Chapter 7. Additionally, the continuous stop task requires validation with respect to the standard SST to establish whether the same underlying construct supports the stopping of actions underway (as in continuous paradigm), compared to those to-be-executed (as in the SST; see Logan & Cowan, 1984; Morein-Zamir *et al.*, 2004). In Study 4 this was impeded by a large number of instances of violations of the independent race model assumptions. This in itself demonstrates an additional benefit of the continuous stop/change task (i.e. in the standard SST, SSRT can only be estimated when the independence assumptions are met; in the continuous task, SSRTs are measured directly so the independence assumptions can be violated). Additional validation could be sought by establishing whether the continuous stop task is sensitive to stimulus-response compatibility and signal presentation probability as established by Morein-Zamir *et al.* (Morein-Zamir *et al.*, 2006, 2007). Modifications are also necessary to make the task suitable for all populations (e.g. including the elderly) and for use in imaging studies.

[126] Re-analysis of data with violations excluded was found to have minimal effect on the interpretability of results, potentially owing to the few violations observed (see APP10.6.2).

8.2. Limitations

While some of the methodological limitations that arose in the studies presented in this thesis have been discussed, I outline further instances below. Here, I discuss these with reference to how they could have influenced the interpretability of my findings and how they can be overcome in future research.

8.2.1. Behavioural measures

In studies 1-3, the pattern of DRT2 across SOAs was indicative of the presence of a PRP (i.e. increased DRT2 at short SOAs relative to long SOAs; Telford, 1931; Welford, 1952; Pashler, 1994) and I made used of a novel quantification procedure to estimate the size and location of the central bottleneck present in dual-task decision making (see Sections 2.3.1). This procedure requires validation and as such it is possible that it may not have been an appropriate method to assess the influence of a structural or strategic bottleneck on behaviour and %BOLD. Validation could be sought by the use of simulations to recover the true bottleneck. Alternatively, subtle manipulation of SOAs (e.g. by using the locus of slack procedure: McCann & Johnston, 1992; Miller & Reynolds, 2003; Pashler, 1994) could be explored to determine the point at which DRT2 plateaus (i.e. where the bottleneck is no longer influential) and comparing the result with that estimated using the quantification procedure over a broader range of SOAs. Such work would be a worthwhile endeavour as the procedure may afford greater precision in identifying central bottleneck processes than is possible by the subtraction of effects between long and short SOAs (see Szameitat *et al.*, 2002) or between dual- and single-task performance (Szameitat, Schubert, Müller & Von Cramon, 2002) as currently used. Test re-test reliability of this technique also needs to be ascertained.

A second issue relates to the use of block-based designs, such as those employed in the context-cueing paradigm and continuous stop/change tasks. Differences in the allocation of attention are apparent when tasks are presented separately (Sebastian *et al.*, 2016) and likely contribute to the number of processes that are not adequately controlled between inhibitory and non-inhibitory action updating tasks. This is particularly true of the context-cueing paradigm, where obvious proactive slowing

occurs in the SST, relative to the DT, even though both tasks require the engagement of goal-directed attention (Aron, 2011; Aron & Verbruggen, 2008; Verbruggen *et al.*, *2*010; Verbruggen & Logan, 2009c; see also Braver, 2012). Proactive slowing does not appear to be as much of an issue in the continuous stop/change task, but additional attention or task-set differences almost certainly remain. This could be overcome in future work by the use of mixed-event designs where both stop and change trials are presented within the same block. However, additional response options upon presentation of signals within a block may increase the potential for additional strategies to be adopted as the signals would be need to differentiated as well as responded to (Bissett & Logan, 2014).

8.2.2. fMRI analyses

ROI-based analyses conducted on fMRI data in Studies 1 and 2 (Chapters 2 and 5) made use of atlas-based masks as means to extract %BOLD from specific regions. While atlases based on group data provide reliable taxonomy of both cortical and subcortical regions, the use of anatomically defined ROIs is preferable (Poldrack, 2007). This is certainly the case when defining the location of anatomically small structures such as those in the BG, particularly if the location is known to be highly variable across individuals (such as the STN and SN; de Hollander et al., 2015). Advancements in imaging techniques and the ability to use high scanning fields (7T and greater) make the identification of such small regions possible, and should be utilised where possible (de Hollander et al., 2015). Furthermore, such techniques may enable functional differentiation to be made within structures (such as the controversial tripartite division of the STN; Alkemade & Forstmann, 2014; Keuken et al., 2012) which can help further delineate the role of the BG in action updating. This is of particular interest to structures with newly proposed roles, such as that of the GP outlined above (Mallet *et al.*, 2016; Saunders *et al.*, *2*015; Chen et al, 2015; Milardi *et al.*, *2*014).

The omission of spatial smoothing kernels in the pre-processing of fMRI data has also been recommended by de Hollander *et al.* (2014). Smoothing kernels essentially blur the BOLD signal across voxels as a means to reduce interference from random noise and enhance the ability to detect true activations (Mikl *et al.*, *2*008; Triantafyllou *et al.*, *2*006; Kamitani & Sawahata, *2*010). In Study 1, a 5mm full-width-

half-maximum Gaussian kernel was used to spatially smooth the data. Although this approach is consistent with previous work (Aron & Poldrack, 2006; Aron *et al., 2*007) and was pre-registered, it can lead to mixing of fMRI signals between structures (de Hollander et al., 2015). Hence, its exclusion from the analysis of the data acquired in Study 2. The anterior spread of activity specifically associated with response inhibition in the rIFG in Study 2 was less pronounced than in Study 1, and may have given a false impression as to the true extent of rIFG recruitment under SST conditions. Given the additional issues regarding the omission of the IT in Study 2 (discussed above) it was not possible to explore how the exclusion of spatial smoothing influenced the consistency between the STN and SN activation within the hypothesised pathways. This, and the exploration of the effect of spatial smoothing on other ROIs, provides an opportunity for future research.

8.2.3. GABA quantification

As noted above, the presence of relationships between GABA concentration, %BOLD and SSRT explored in Study 2 proved inconclusive. As discussed in Chapter 4, it is possible that this uncertainty arises from the unreliability of spectral quantification in the frontal lobes. Towards the front of the head, the magnetic field becomes inhomogeneous due to the presence of the sinuses and magnetic susceptibility differences between brain tissue and air. This problem can be overcome by the inclusion of manual shimming techniques which act to minimise this inhomogeneity (de Graaf, 2007).

As discussed in APP10.3.3, the quantification of GABA can also be problematic due to the complex spectral pattern of GABA (due to J-coupling) and the overlap in the GABA spectrum with other molecules (Waddell *et al., 2*007; Puts & Edden, 2012; Mullins *et al., 2*014). To improve GABA quantification, MRS spectra could be acquired at higher magnetic fields which aid the identification of metabolites in MRS spectra (Mullins *et al.,* 2014; Puts & Edden, 2012). An additional advantage of acquiring MRS data at higher field strengths is the ability to quantify additional metabolites, including glutamate, which interacts with GABA to maintain the excitatory-inhibitory balance with the brain (Isaacson & Scanziani, 2011). This could provide important insights into how actions are supported.

8.2.5. Psycho-physiological measures

The psycho-physiological methods explored in Study 3 are characterised by substantial variability and may not have been sensitive enough to detect subtle differences (Sirois & Brisson, 2014; van Steenbergen & Band, 2013) in response control demands associated with the sub-tasks comprising the context-cueing paradigm. While some differences between tasks were detected in the cardio-respiratory analyses in Study 1 (increased cardiac and respiration rate in the DT), these were not robust and were not replicated in the data acquired during Study 2. This may be due to the simple motoric tasks comprising the context-cueing paradigm relative to the more demanding tasks employed in other work[127] (e.g. mental arithmetic computation, memory-tasks, driving and flying; e.g. Beatty & Kahneman, 1966; Kahneman, *et al.,* 1967; Piquado *et al.,* 2010; Veltman and Gaillard, 1998).

However, there were some interesting patterns in the data, and I would recommend future research to include a baseline (control) task and/or self-report measures to interpret unexpected findings. For example, in Chapter 6, cardio-respiratory measures were analysed as it was expected that rates would increase with task demands as per previous work (e.g. Backs *et al.,* 1991; Backs & Seljos, 1994; Carroll *et al.,* 1986; Chen *et al.,* 2015; Fairclough & Houston, 2004; Fairclough *et al.,* 2005; Wientjes, 1992). However, no difference in these measures was found between the SST and IT in Study 1. This was unexpected given the requirement to update an ongoing action plan in the SST and not in the IT. Furthermore, pupil diameter was expected to increase with mental effort and error-likelihood in Study 3, but was found to negatively (although inconclusive) correlate with reports of SST-related difficulty and frustration. Collectively, these findings indicate the potential for a slowing of autonomic nervous system activity under SST conditions[128]. Indeed, such slowing has been established in cardiac measures on unsuccessful signal trials in both SST and go/no-go tasks (van Boxtel *et al.,* 2005; van Boxtel & Van der Molen, 2001; Jennings *et al.,* 1990, 1992). Thus comparison between the SST and control tasks may be used to incorrectly infer the SST is less demanding. Certainly, self-report measures (and informative baseline

[127] In Study 2, the omission of the IT may have also decreased the demands across the context-cueing paradigm.

[128] The potential role of acetylcholine and norepinipherine in the top-down control of pupil diameter (Yu, 2012; Yu & Dayan, 2005) also requires exploration in future work where pupilometry is used in the study of action control.

tasks) are easily incorporated and may assist interpretation of results that are inconsistent with expectations.

8.3. Conclusion

The overarching aim of this thesis was to establish whether a specialised prefrontal network operates exclusively to support motor inhibition or instead supports general processes involved in the updating of action plans. Collectively, my findings indicate widespread fronto-parietal activity supporting action updating, with evidence pointing moderately toward a specialised role of the rIFG in response inhibition. The rIFG appears to exert top-down control over right-lateralised BG in implementing response inhibition. It is possible that the mechanisms by which the rIFG exerts its effects could be GABAergic, which could act to facilitate response selection when there is competition amongst alternative representations. However, more work is required to confirm or refute these possibilities. Furthermore, while the studies presented in this thesis attempted to better control for non-inhibitory processes, it remains unclear what the exact processes regions involved in action updating support. Does the rIFG act to implement response inhibition directly? Or to resolve competition between response options? To better inform these questions it is essential that we control more stringently for non-inhibitory processes required to successfully perform the SST. The continuous stop/change task shows potential, although further development is necessary to establish the conditions under which a successful change could occur in the absence of inhibition.

9. References

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10. Appendices

10.1. Appendices for Chapter 2.

APP10.1.1. MRI and TMS screening forms

CUBRIC, CARDIFF UNIVERSITY - MAGNETIC RESONANCE IMAGING UNIT INITIAL SCREENING FORM

NAME OF PARTICIPANT …… Sex: M / F

Date of birth……

CUBRIC UNIQUE IDENTIFIER:……

Please read the following questions CAREFULLY and provide answers. For a very small number of individuals, being scanned can endanger comfort, health or even life. The purpose of these questions is to make sure that you are not such a person. You have the right to withdraw from the screening and subsequent scanning if you find the questions unacceptably intrusive. The information you provide will be treated as strictly confidential and will be held in secure conditions.

If you are unsure of the answer to any of the questions, please ASK the person who gave you this form or the person who will be performing the scan. Definitions of some of technical terms are given overleaf.

Please answer all	*Circle*
1. Have you been fitted with a pacemaker, or any other implanted device?	YES/NO
2. Have you any surgical clips, aneurysm clips, shunts or stents in your body?	YES/NO
3. Have you had a heart valve replacement	YES/NO
4. Have you ever had any metal fragments in your eyes?	YES/NO
5. Have you had a cochlear implant fitted	YES/NO
6. Do you wear a hearing aid?	YES/NO
7. Do you have any other mechanical/electrical or magnetically operated devices in or on your body?	YES/NO
8. Have you ever had any metal fragments, e.g. shrapnel in any other part of your body?	YES/NO
9. Have you any surgically implanted metal in any part of your body (e.g. joint replacement or bone reconstruction, pins, rods, screws, nails, clips, plates, wires).	YES/NO
10. Have you ever had any surgery that might have involved metal implants of which you are not aware?	YES/NO
11.Do you have a catheter fitted?	YES/NO
12.Do you have any intra-venous devices fitted (including stents and filters)	YES/NO
13. Do you have any Tattoos?	YES/NO
14. Is there any possibility that you might be pregnant?	YES/NO
15. Have you been sterilised using clips?	YES/NO
16. Do you have a contraceptive coil (IUD) installed?	YES/NO

17. Do you have **any** dental work (including dentures, crowns, bridgework, braces) in your mouth, other than simple fillings?	YES/NO
18. Have you ever suffered from any of: epilepsy, diabetes or thermoregulatory problems?	YES/NO
19. Have you ever suffered from any heart disease?	YES/NO
20. Do you have any permanent eye makeup?	YES/NO

I have read and understood the questions above and have answered them correctly.

SIGNED…… DATE……

In the presence of …….. (Name) …….. (Signature)

CUBRIC, CARDIFF UNIVERSITY - TMS and TDCS SCREENING FORM

NAME OF PARTICIPANT …… **Sex: M / F**

Left or right handed? ……

Date of birth……

Have you previously had an MRI scan at CUBRIC? ……

If so, are you happy for us to access your existing CUBRIC MRI data in this study? ……..

Do you normally wear glasses or contact lenses? (please indicate which)……..

Do you have normal colour vision? …….

Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (TDCS) are methods for safely stimulating the brain using an electric current.

Before receiving TMS or TDCS, please read the following questions carefully and provide answers. For a small number of individuals, these techniques may carry an increased risk of causing a seizure or other symptoms. The purpose of these questions is to make sure that you are not such a person. You have the right to withdraw from the screening and subsequent scanning if you find the questions unacceptably intrusive. The information you provide will be treated as strictly confidential and will be held in secure conditions.

If you are unsure of the answer to any of the questions, please ask the person who gave you this form or the person who will be performing the study. Definitions of some of technical terms are given overleaf.

	Please tick
Have you ever had an adverse reaction to TMS, TDCS, or other form of brain stimulation?	☐Yes ☐No
Do you experience claustrophobia?	☐Yes ☐No
Have you or has anyone in your family had a seizure?	☐Yes ☐No
Have you had a stroke?	☐Yes ☐No
Have you had a serious head injury (including neurosurgery) or have you ever been taken to hospital following an injury to the head?	☐Yes ☐No
Do you have any metal in your head (outside the mouth) such as shrapnel, surgical clips, or fragments from welding or metalwork?	☐Yes ☐No
Do you have any implanted devices such as cardiac pacemakers, aneurysm clips, cochlear implants, medical pumps, deep brain stimulators, or intracardiac lines?	☐Yes ☐No
Do you suffer from frequent or severe headaches or have you ever experienced a migraine?	☐Yes ☐No
Have you ever had any other brain-related condition?	☐Yes ☐No
Have you ever had any illness that caused brain injury?	☐Yes ☐No
Are you taking any psychiatric or neuroactive medications (e.g. antidepressants), or do you have a history of drug abuse?	☐Yes ☐No

Are you pregnant?	☐Yes ☐No
Do you, or does anyone in your family, have epilepsy?	☐Yes ☐No
Are you taking any medication, or suffering from any medical condition, that causes dizziness, nausea or balance problems?	☐Yes ☐No
Do you suffer from eczema or any other acute skin condition?	☐Yes ☐No
Do you hold a heavy goods vehicle driving license, pilot's license, or bus license?	☐Yes ☐No

I have read and understood the questions above and have answered them correctly.

SIGNED…… DATE……

In the presence of …….. (Name) …….. (Signature)

TMS and TDCS Pre-Session Screening

To minimise the risk of TMS causing an adverse effect, it is important that you answer the following questions accurately before we begin the session.

---

1) In the last 12 hours, have you consumed more than 3 units of alcohol or any recreational drugs?

☐Yes ☐No

---

2) Did you get a good night's sleep last night, and do you feel alert?

☐Yes ☐No

---

3) In the last two hours, have you consumed more than two cups of coffee or any other caffeinated drinks?

☐Yes ☐No

Date…….

Name…….

Signature…….

APP10.1.2. Task instructions.

Instructions (main): these instructions were given to participants prior to training on each sub-task comprising the context-cueing paradigm and prior to the testing session.

Throughout the experiment you will be presented with white arrows that will appear at the centre of the screen. Your task is to respond to the direction of the arrow as fast and as accurately as possible.

For arrows pointing left <<< you must respond by pressing the button beneath your index finger on your right hand.

For arrows pointing right >>> you must respond by pressing the button beneath your middle finger on your right hand.

Between the arrows you will be presented with a + for a short, but variable, duration. Do not respond to this.

On some occasions the white arrows will turn **black** after a **variable** delay. This is a **signal** and will act as an instruction for you to alter your response to the arrow in different ways, depending on the task instruction you are given. Instructions for how you should respond to signals will be provided at the beginning of each test block, with either the words STOP, DOUBLE or IGNORE. It is important that you remember the task instruction as you will have no reminder.

For **STOP** blocks, when you see the signal you must try to stop your response (i.e. try not to respond to the direction of the arrow). You will notice that on some trials it will be relatively easy to stop, whereas on others it will be more difficult. It is expected that you will get some wrong. Nevertheless, it is important to keep responding as quickly as possible to the direction of the white arrows, and to try to stop this response if you see a black signal.

For **DOUBLE** blocks, when you see the signal you must respond by pressing the button beneath your thumb on your right hand after you have responded to the direction of the arrow. Remember that your primary task is to respond to the direction of the arrow first, and that making the thumb press is a secondary response, only to be made if you see the signal. It is important your first response is made as fast and as accurate as possible. Your second response should also be made as fast and as accurately as possible. You will notice that it will be relatively easy to make the second response on some trials, whereas it will be more difficult for others.

For **IGNORE** blocks you must ignore the signal and respond to the direction of the arrows as you would if the signals were not present. Again, it is important that you respond as fast and as accurately as possible to all trials.

The presentation of signals is random and they will not occur in any predictable order. It is important that you remember to respond as fast and as accurately as possible to all arrows and that you do not wait for a signal to appear.

The cue STOP, DOUBLE or IGNORE will be presented for 7 seconds before the beginning of the next trial.

Remember: it is important that you respond as quickly and as accurately as possible at all times and that you do not wait for signals to appear.

A brief reminder of the overall instructions will appear on the screen before the experiment begins, but please ask the experimenter if you have any questions.

Instructions (brief): these instructions were presented on the screen prior to each behavioural run in the testing session and before each run during mixed training in the training session.

Respond to the direction of the arrows

Use your index finger to respond to <<<

Use your middle finger to respond to >>>

On signal trials the colour of the arrow will change

STOP= try to stop your response

DOUBLE= execute 2nd respond using your thumb after 1st response

IGNORE= ignore the signal and respond as normal

APP10.1.3. Pre-set exclusion criteria.

Exclusion criteria were set prior to data collection and are outlined below.

APP10.1.3.1. Exclusions based on behavioural measures.

1. If accuracy on no-signal trials fell below 85%; measured separately for each context, regardless of arrow direction.
2. If accuracy on ignore-signal or double-signal trials fell below 85%; measured separately for each context, regardless of arrow direction.
3. If successful inhibition on stop-signal trials fell below 25% or above 75%.
4. If 'grouping' of responses was observed on 11% double-signal trials.
5. If mean no-signal RTs exceeded 500ms in the double and ignore tasks or 600ms in stop task.
6. If mean RTs for signal trials exceeded 500ms in the double and ignore tasks.

7. If a participant's no-signal RTs were more than 2.5 standard deviations from the group level mean as these participants would be deemed as slow responders; measured for each context separately across all no-signal trials regardless of arrow direction.

APP10.1.3.2. Additional reasons for exclusion.

8. Unanticipated technical failures, including any of the hardware used for stimulus presentation, unforeseen failure of scanner components or failure of any of the physiological monitoring equipment. Note that fieldmaps were acquired at a later date if compromised.

9. Gross MR artefacts present in any of the imaging data that may affect identification of regions of activation and / or registration (including warping, ghosting and banding).

10. For each participant, if head movement resulted in translational movement exceeding 1 voxel in any direction for a specific run then corresponding fMRI data will be excluded from analysis. If excessive motion was detected on 2 runs or more then all participant data was excluded.

11. If at any point, participants failed to meet the MR and TMS safety guidelines.

12. Participants could voluntarily withdraw from the study for any reason.

APP10.1.4. Results.

Reported here are the results of analyses conducted subsequent to outlier exclusion and non-parametric tests (if applicable). Parametric tests without outlier removal are reported in the main text. Discrepancies between results are discussed in the main text.

APP10.1.4.1. Imaging results.

APP10.1.4.1.1. One sample t-tests were conducted to establish whether %BOLD in the rIFG was reliably greater than 0 for the signal>no-signal contrasts for each task context.

SST: $t_{(28)}$=8.31, p<.001, BF=2.54^{e+6}; IT: $t_{(27)}$=7.3, p<.001, BF=197321).

APP10.1.4.1.2. Subsequent to outlier exclusion, the repeated measures ANOVA between pre-SMA and rIFG activity under different task conditions revealed a significant main effect of ROI ($F_{(1,26)}$=8.6, p=.007, BF=3.17), in which rIFG was recruited to a significantly greater extent than the pre-SMA. A main effect of task ($F_{(2,52)}$=6.2, p=.004, BF=98.25), revealed that action updating in the SST led to increased %BOLD across ROIs relative to the IT ($p_{.0167}$=.002, BF=20.15), although no other differences were observed (all p>.069 all BF<0.96). An interaction effect between task and ROI was also revealed ($F_{(2,52)}$=3.74, p=.031, BF=0.63), which was the result of differences in recruitment under different task conditions in the rIFG (SST vs. DT: $p_{.025}$=.002, BF=20.13; SST vs. IT: $p_{.0167}$<.001, BF=74.6; DT vs. IT: p=.342, BF=0.31) but not the pre-SMA (SST vs. DT: p=.866, BF=0.21; SST vs. IT: p=.043, BF=1.41; DT vs. IT: $p_{.0167}$=.041, BF=1.45).

APP10.1.4.1.3. Subsequent to outlier exclusion a repeated measures ANOVA between *pars opercularis* and *pars triangularis* activity under different response control tasks revealed a main effect of ROI ($F_{(1,27)}$=53.86, p<.001, BF=93022.94), owing to greater *pars opercuaris* relative to *pars triangularis* activity. A main effect of task ($F_{(2,54)}$=13.89, p<.001, BF=240084.61) revealed greater activity associated with action updating in the SST relative to the DT ($p_{.025}$<.001, BF=91.44) and IT ($p_{.0167}$<.001, BF=222.52), but no difference between action updating in the DT and the IT (p=.309, BF=0.20). These main effects were qualified by an interaction between ROI and task ($F_{(2,54)}$=9.61, p<.001, BF=2.28). Here, the *pars opercularis* was found to be recruited to a significantly greater extent under SST relative to DT ($p_{.025}$=.004, BF=9.16) and IT ($p_{.0167}$<.001, BF=1042.81) conditions, and under DT relative to IT ($p_{.05}$=.005, BF=8.44) conditions. The *pars triangularis* was found to be recruited to a significantly greater extent under SST relative to DT ($p_{.0167}$<.001, BF=94.63) and IT ($p_{.025}$=.003, BF=12.17) conditions, but there was not difference in the recruitment of this region when action updating was required in the DT relative to no updating in the IT (p=.23, BF=0.4).

APP10.1.4.2. Brain-behaviour relationships

A series of analyses were conducted to establish if there were any relationships between %BOLD in cortical structures acquired from the signal>no-signal contrasts in the SST and DT with behavioural indices of action updating. In the SST, ROIs interrogated were the right and left pre-SMA, right and left IFG, right *pars opercularis*, and right *pars triangularis*. In the DT, ROIs interrogated where the right and left pre-SMA and the right and left IFG.

APP10.1.4.2.1. Relationships between indices of inhibitory action updating and %BOLD

APP10.1.4.2.1.1. Correlations between %BOLD, SSRT and proactive slowing

Table APP10.1.1. Correlations between %BOLD in cortical ROIs acquired from the contrast stop signal>stop no-signal with SSRT and proactive slowing.

	Mean SSRT				Integration SSRT				Proactive Slowing^{+}			
ROI	r	df	*p*	BF	r	df	*p*	BF	r	df	*p*	BF
R IFG	0.1	26	.618	0.23	0.26	25	.186	0.46	-0.3	25	.128	0.61
R preSMA	0.21	26	.283	0.35	0.16	25	.437	0.27	0.14	25	.48	0.26
L IFG	-0.18	26	.369	0.3	-0.16	26	.403	0.27	0.1	25	.639	0.23
L preSMA	-0.01	26	.948	0.2	0.13	25	.515	0.25	0.1	26	.63	0.23
R pars op	0.08	27	.681	0.21	0.21	26	.296	0.35	-0.26	24	.194	0.45
R pars tri	0.08	26	.689	0.22	0.25	25	.213	0.43	-0.2	26	.312	0.33

Note. Stop signal reaction time (**SSRT**) was estimated using the mean and integration methods, separately. **ROI**=region of interest; **r=**Pearson's correlation coefficient; **df**= degrees of freedom; ***p***= *p*-value; **BF**=Bayes Factor; **R**=right; **L**=left; **IFG**=inferior frontal gyrus; **preSMA**=pre-supplementary motor area**; pars op**= pars opercularis; **pars tri**= pars triangularis; $^{+}$= computed on transformed data. α-level not shown as all *p*>.05.

APP10.1.4.2.1.2. Re-analysis of %BOLD with SSRT subsequent to median split

Table APP10.1.2 Differences in %BOLD in cortical ROIs between participants with short vs. long SSRTs. Independent t-tests were conducted subsequent to median split of SSRT.

	Mean SSRT				Integration SSRT			
ROI	t	df	*p*	BF	t	df	*p*	BF
R IFG	-0.91	25	.371	0.49	-0.93	27	.36	0.48
R preSMA	-0.7	26	.493	0.42	1.6	24	.122	0.92
L IFG$^{++◊◊}$	-0.13	17.28	.898	0.36	0.08	19.36	.939	0.35
L preSMA	-0.21	25	.838	0.36	-0.34	27	.74	0.36
R pars op$^{◊}$	-1.01	25	.321	0.52	-1.49	18.22	.154	0.73
R pars tri	-1.23	26	.229	0.62	-1.18	28	.249	0.58

Note. Stop signal reaction time (**SSRT**) was estimated using the mean and integration methods, separately. When using the mean method, 2 participants SSRT were identical to the median value and were excluded. **ROI**=region of interest; **t=**t-value; **df**= degrees of freedom (corrected where Levene's test for homoscedacity significant); ***p***=p-value; **BF**=Bayes Factor; **R**=right; **L**=left; **IFG**=inferior frontal gyrus; **preSMA**=pre-supplementary motor area**; pars op**= pars opercularis; **pars tri**= pars triangularis; $^{◊}$=conducted on transformed data when SSRT was estimated using the integration method; $^{++}$ and $^{◊◊}$=non-parametric analysis required when SSRT was estimated using the mean and integration methods, respectively. α-level not shown as all *p*>.05.

Non-parametric Mann-Whitney U tests were required to establish whether %BOLD in the left IFG was different at short vs. long SSRTs (as established by median split).

Mean method: U=114, N=28, *p*=.482. Subsequent to outlier exclusion: U=100, N=27, *p*=.685.

Integration method: U=119, N=30, *p*=.806. Subsequent to outlier exclusion: U=104, N=29, *p*=.983.

APP10.1.4.2.1.3. Correlations between %BOLD and SSD and %BOLD pre- vs. post- 50%SSD.

Correlation analyses were computed to establish the %BOLD in relation to the SSD in the SST. 6 delays (SSDs) were used for each behavioural run. As within-subject data were highly correlated, separate analyses were conducted for each participant and each ROI separately. Here, non-parametric Spearman's rho was used for the correlation

analyses. Resultant coefficients were then subjected to Frequentist one-sample t-tests to ascertain whether there was an effect of increasing delay between stimulus and signal.

Paired sample t-tests in relation to signal onset (pre-vs. post-50%SSD) are also reported.

Table APP10.1.3. One-sample t-tests of coefficients yielded from within-subject correlations across SSD and paired sample t-tests between %BOLD when stop signals were presented before or after the 50%SSD.

	Correlation SSD			Pre vs. post 50%SSD				
ROI	t	*p*	α	t	df	*p*	α	BF
R IFG	1.33	.194		-1.91	28	.067		0.97
R preSMA	**2.96**	.006	.0028	**-3.99**	28	<.001	.0028	**69.57**
L IFG	0.44	.663		0.35	29	.732		0.21
L preSMA	2.18	.037		-1.63	28	.115		0.64
R pars op	2.06	.048		**-2.97**	28	.006	.0033	**6.91**
R pars tri	-0.41	.684		0.31	29	.756		0.2

Note. For **correlation SSD**: as within-subject data were highly correlated, separate correlations were conducted for each participant and each ROI separately. Resultant Spearman's rho were then subjected to Frequentist one-sample t-tests to ascertain whether there was an effect of increasing delay between stimulus and signal. **Pre- vs. post 50%SSD** refers to the results of paired sample t-tests when signals were presented before or after the 50%SSD (subsequent to outlier exclusion). **ROI**=region of interest; **t=**t-value, significant t-values are reported in bold; **df** =degrees of freedom (df=29 for correlation SSD analyses); ***p***=*p*-value; **α**=alpha level; **BF**=Bayes Factor, BFs>3 are reported in bold; **R**=right; **L**=left; **IFG**=inferior frontal gyrus; **preSMA**=pre-supplementary motor area**; pars op**= pars opercularis; **pars tri**= pars triangularis. Holm-Bonferonni correction was computed for all ROI analyses- including those reported in Table APP10.2.3. α calculated as: α(*k*)=0.05/(*n*-*k*+1), where *n* is the number of ROIs (in this case 18), and *k* is the rank ordering of *p*-values from 1 to *n.*

APP10.1.4.2.2. Relationships between indices of non-inhibitory action updating and %BOLD

APP10.1.4.2.2.1. Correlations between %BOLD, DRT2 and the size of the decision bottleneck.

Table APP10.1.4. Correlations between %BOLD in cortical ROIs acquired from the contrast double signal>double no-signal with DRT2 and estimated size of the PRP.

	DRT2					Size			
ROI	r	df	*p*	α	BF	r	df	*p*	BF
R IFG	-0.17	27	.393		0.28	0.35	27	.059	1.02
R preSMA	-0.31	26	.111		0.68	-0.01	26	.95	0.2
L IFG	-0.14	28	.473		0.25	0.28	27	.145	0.55
L preSMA	-0.39	25	.044	.0031	1.38	0.01	26	.945	0.2

Note. **DRT2**=the latency of the non-inhibitory action updating process; **Size**=size of the decision bottleneck; **ROI**= region of interest; **r=** Pearson's correlation coefficient; **df**= degrees of freedom; ***p***=p-value; **α**=alpha level; **BF**=Bayes Factors; **R**=right; **L**=left; **IFG**=inferior frontal gyrus; **preSMA**=pre-supplementary motor area**.** Holm-Bonferonni correction was computed for all ROI analyses- including those reported in Table APP10.2.5. α calculated as: α(*k*)=0.05/(*n*-*k*+1), where *n* is the number of ROIs (in this case 16), and *k* is the rank ordering of *p*-values from 1 to *n.*

APP10.1.4.2.2.2. Re-analysis of %BOLD with DRT2 and the size of the decision bottleneck

Table APP10.1.5. Differences in %BOLD in cortical ROIs between participants with short vs. long DRT2s and small vs. large PRPs. Independent t-tests were conducted subsequent to median split of DRT2 and size of PRP, separately.

	DRT2				Size			
ROI	t	df	*p*	BF	t	df	*p*	BF
R IFG	1.59	24.23	.124	0.88	-1.23	25	.229	0.63
R preSMA	1.48	27	.151	0.78	0.93	24	.927	0.36
L IFG	0.6	28	.555	0.39	-1.61	25	.119	0.38
L preSMA	1.52	20.13	.144	0.77	-0.44	25	.661	0.39

Note. 3 participants size of the decision bottleneck corresponded to the estimated median size and were excluded from these analyses prior to further outlier exclusion. **DRT2=** the latency of the non-inhibitory updating process; **Size=**size of the decision bottleneck; **ROI**= region of interest, **t=** t-value; **df**=degrees of freedom (adjusted where Levene's test for homoscedascity was significant); ***p***=p-value; **α**= alpha level; **BF**=Bayes Factors, BFs>3 are reported in bold; **R**=right; **L**=left; **IFG**=inferior frontal gyrus; **preSMA**=pre-supplementary motor area. Holm-Bonferonni correction was computed for all ROI analyses- including those reported in Table APP10.2.6. α

calculated as: α(*k*)=0.05/(*n*-*k*+1), where *n* is the number of ROIs (in this case 16), and *k* is the rank ordering of *p*-values from 1 to *n.*

APP10.1.4.2.2.3. Correlations between %BOLD and SOA and %BOLD pre- vs. post- decision bottleneck.

Correlation analyses were computed to establish the %BOLD in relation to the SOA in the DT. 6 delays (SOAs) were used for each behavioural run. As within-As within-subject data were highly correlated, separate analyses were conducted for each participant and each ROI separately. Here, non-parametric Spearman's rho was used for the correlation analyses. Resultant coefficients were then subjected to Frequentist one-sample t-tests to ascertain whether there was an effect of increasing delay between stimulus and signal.

Paired sample t-tests in relation to signal onset (pre-vs. post decision bottleneck) are also reported.

Table APP10.1.6. One-sample t-tests of coefficients yielded from within-subject correlations across SOAs and paired sample t-tests between %BOLD when double signals were presented within or post decision bottleneck.

	Correlation SOA			Pre vs. post				
ROI	t	*p*	α	t	df	*p*	α	BF
R IFG^{++}	1.04	.308		-1.6	28	.121		0.61
R preSMA	2.32	.028		**-3.19**	29	.003	.0031	**11.34**
L IFG^{++}	-1.57	.128		0.17	28	.865		0.2
L preSMA^{++}	2.63	.014	0.0031	-3.13	28	.004		**9.73**

Note. For **correlation SOA**: as within-subject data were highly correlated, separate correlations were conducted for each participant and each ROI separately. Resultant Spearman's rho were then subjected to either Frequentist or Bayesian one-sample t-tests to ascertain whether there was an effect of increasing delay between stimulus and signal. Corresponding degrees of freedom=29. **Pre- vs. post 50%SSD** refers to the results of paired sample t-tests when signals were presented before or after the 50%SSD. **ROI**=region of interest; **t=**t-value, significant t-values are reported in bold; ***p***=*p*-value; **α**= alpha level; **BF**=Bayes Factor, BFs>3 are reported in bold; **R**=right; **L**=left; **IFG**=inferior frontal gyrus; **preSMA**=pre-supplementary motor area**;** $^{++}$= non-parametric analysis required. Holm-Bonferonni correction was computed for all ROI analyses- including those reported in Table APP10.2.7. α calculated as: α(*k*)=0.05/(*n*-*k*+1), where *n* is the number of ROIs (in this case 16), and *k* is the rank ordering of *p*-values from 1 to *n.*

Non-parametric Wilcoxon rank sum tests were computed to establish whether were required to establish there were differences in rIFG or left IFG and left pre-SMA recruitment prior to or post decision bottleneck.

Table APP10.1.7. Non-parametric Wilcoxon rank sum tests for pre- vs. post decision bottleneck, with and without outlier exclusion.

	No exclusions			With exclusions		
ROI	Z	N	*p*	Z	N	*p*
R IFG	1.76	30	.079	1.52	29	.127
L IFG	-0.09	30	.926	-0.42	29	.673
L preSMA	2.95	30	.003	2.78	29	.005

Note. **ROI**= region of interest; **Z**= standardized score; **N**= number of participants; ***p***=p-value; **R IFG**= right inferior frontal gyrus; **L pre-SMA**= left pre-supplementary motor area.

APP10.1.4.2.3. Lateralization of action updating

Paired sample t-tests were computed to establish whether activity in right or left hemispheres was greater under inhibitory and non-inhibitory action updating conditions.

Table APP10.1.8. Paired sample t-tests between right and left ROIs under inhibitory and non-inhibitory action updating conditions

Contrast	ROI	Hemisphere	t	df	*p*	α	BF
Stop signal>	IFG	Right	**8.38**	27	<.001	.0063	**2.29^{e+06}**
stop no-signal	pre-SMA	Right	**6.76**	29	<.001	.0071	**77430.59**
Double-signal>	IFG	Right	**5.52**	29	<.001	.0063	**3417**
double no-signal	pre-SMA	Right	**5.32**	29	<.001	.0071	**2007**

Note. **ROI**= region of interest; **Hemisphere**= the hemisphere for which the corresponding ROI demonstrated the greatest %BOLD; **t**=t-value, significant t-values are reported in bold; **df**= degrees of freedom; ***p***=p-value; **α**= alpha level; **BF**=Bayes Factors, BFs>3 are reported in bold; **IFG**=inferior frontal gyrus; **preSMA**=pre-supplementary motor area. Holm-Bonferonni correction was computed for all ROI analyses- including those reported in Table APP10.2.9. α calculated as: $\alpha(k)=0.05/(n-k+1)$, where n is the number of ROIs (in this case 8), and k is the rank ordering of p-values from 1 to n.

10.2. Appendices for Chapter 3.

APP10.2.1. Brain-behaviour analyses

Reported here are the results of analyses conducted subsequent to outlier exclusion and non-parametric tests (if applicable). Parametric tests without outlier removal are reported in the main text. Discrepancies between results are discussed in the main text.

A series of analyses were conducted to establish if there were any relationships between %BOLD in subcortical structures acquired from the signal>no-signal contrasts in the SST and DT with behavioural indices of action updating. In both the SST and DT, ROIs interrogated were the right and left STR, GPe. GPi, STN, SN and THAL.

APP10.2.1.1. Relationships between indices of inhibitory action updating and %BOLD

APP10.2.1.1.1. Correlations between %BOLD, SSRT and proactive slowing

Table APP10.2.1. Correlations between %BOLD in subcortical ROIs acquired from the contrast stop signal>stop no-signal with SSRT and proactive slowing.

	Mean SSRT				Integration SSRT					Proactive Slowing^{+}			
ROI	r	df	*p*	BF	r	df	*p*	α	BF	r	df	*p*	BF
R STR	0.2	25	.319	0.33	0.26	24	.194		0.45	-0.15	26	.457	0.26
R GPe	0.36	26	.064	1.07	0.4	25	.041	.0028	1.53	-0.08	26	.692	0.22
R GPi	0.15	25	.453	0.26	0.09	25	.659		0.22	0.02	27	.934	0.2
R STN	-0.32	26	.1	0.74	-0.37	26	.051		1.12	0.15	27	.440	0.26
R SN^{++}	0.04	26	.835	0.2	0.05	24	.794		0.21	0.27	27	.164	0.51
R THAL^{+}	-0.16	26	.426	0.27	-0.25	25	.203		0.43	-0.01	26	.966	0.2
L STR	0.29	25	.141	0.56	0.24	25	.221		0.4	0.06	26	.756	0.21
L GPe	0.36	26	.058	1.07	0.34	26	.074		0.88	0.19	26	.326	0.31
L GPi	0.05	26	.817	0.21	0.08	25	.695		0.22	0.15	26	.436	0.26
L STN^{+}	0.02	27	.911	0.2	0.08	26	.677		0.22	-0.18	27	.340	0.3
L SN^{++}	0.3	27	.119	0.64	0.36	26	.063		1.07	0.29	27	.124	0.59
L THAL	<.01	27	.988	0.2	0.13	26	.501		0.25	0.22	27	.258	0.37

Note. Stop signal reaction time (**SSRT**) was estimated using the mean and integration methods, separately. **ROI**=region of interest; **r**=Pearson's correlation coefficient; ***p***= *p*-value; **α**=alpha level; **BF**=Bayes Factor; **R**=right; **L**=left; **STR**= striatum; **GPe**= globus pallidus externa; **GPi**= globus pallidus interna; **STN**= subthalamic nucleus; **SN**= substantia nigra; **THAL**= thalamus; $^{+}$= computed on transformed data; $^{++}$= non-parametric required. All degrees of freedom=28. Note that Holm-Bonferonni correction was computed for all ROI analyses- including those reported in Table APP10.1.1). α calculated as: α(*k*)=0.05/(*n*-*k*+1), where *n* is the number of ROIs (in this case 18), and *k* is the rank ordering of *p*-values from 1 to *n.*

Non-parametric Spearman's rho was conducted for the LSN and RSN.

RSN and SSRT estimated via the mean method: $rs_{(28)}$=0.05, *p*=.784. Subsequent to outlier exclusion: $rs_{(26)}$=0.04, *p*=.84.

RSN and SSRT estimated via the integration method: $rs_{(28)}$=0.04, *p*=.836. Subsequent to outlier exclusion: $rs_{(24)}$=0.1, *p*=.633.

RSN and proactive slowing: $rs_{(28)}$=0.23, *p*=.231. Subsequent to outlier exclusion: $rs_{(27)}$=0.33, *p*=.078.

LSN and SSRT estimated via the mean method: $rs_{(28)}$=0.31, *p*=.098. Subsequent to outlier exclusion: $rs_{(27)}$=0.24, *p*=.21.

LSN and SSRT estimated via the integration method: $rs_{(28)}$=0.29, *p*=.118. Subsequent to outlier exclusion: $rs_{(26)}$=0.35, *p*=0.071.

LSN and proactive slowing $rs_{(28)}$=0.23, *p*=.226. Subsequent to outlier exclusions: $rs_{(27)}$=0.33, *p*=.077.

APP10.2.1.1.2. Re-analysis of %BOLD with ROIs subsequent to median split

Table APP10.2.2. Differences in %BOLD in subcortical ROIs between participants with short vs. long SSRTs. Independent t-tests were conducted subsequent to median split of SSRT.

	Mean SSRT					Integration SSRT				
ROI	t	df	*p*	α	BF	t	df	*p*	α	BF
R STR$^{++◊◊}$	-2.26	25	.033		2.16	-1.98	19.14	.062		1.28
R GPe$^{++◊◊}$	-2.63	25	.014	.0028	**3.9**	-2.59	27	.015		**3.71**
R GPi	-0.45	14.9	.658		0.4	-0.08	19.52	.938		0.36
R STN$^{++◊◊}$	-0.17	19.34	.864		0.37	1.9	24	.07		1.31
R SN$^{++◊}$	-0.54	23	.592		0.41	1.04	21	.309		0.56
R THAL	-1.54	24	.136		0.86	-0.89	26	.387		0.47
L STR$^{◊◊}$	-1.36	24	.188		0.71	-1.51	18.76	.147		0.75
L GPe	-2.56	26	.017		**3.49**	-2.72	28	.011	.0028	**4.66**
L GPi	-1.42	25	.167		0.75	-1.07	27	.292		0.54
L STN$^{+◊◊}$	-.474	20.14	.64		0.4	0.01	19.78	.990		0.36
L SN$^{++◊◊}$	-1.76	18.77	.095		1.04	-2.32	23.72	.029		2.25
L THAL	-1.39	25	.176		0.73	-1.29	19.35	.212		0.63

Note Stop signal reaction time (**SSRT**) was estimated using the mean and integration methods, separately. 2 participants SSRT were equal to the median value when estimated using the mean method and were excluded. **ROI**=region of interest; **t=**t-value; **df**=degrees of freedom (corrected where Leven's test for homoscedascity was significant); ***p***=*p*-value; **α**=alpha level; **BF**=Bayes Factor, BF>3 reported in bold; **R**=right; **L**=left; **STR**=striatum; **GPe**=globus pallidus externa**; GPi**= globus pallidus interna; **STN**= subthalamic nucleus; **SN**=substantia nigra; **THAL**=thalamus; $^{+}$ and $^{◊}$=analysis conducted on transformed data; $^{++}$ and $^{◊◊}$=non-parametric analysis required when SSRT was estimated using the mean and integration methods, respectively. Holm-Bonferonni correction was computed for all ROI analyses- including those reported in Table APP10.1.2. α calculated as: α(*k*)=0.05/(*n*-*k*+1), where *n* is the number of ROIs (in this case 18), and *k* is the rank ordering of *p*-values from 1 to *n.*

Table APP10.2.3. Non-parametric Mann-Whitney U tests conducted on %BOLD acquired from the stop signal>stop no-signal contrast subsequent to median split of SSRT.

	Mean SSRT					Integration SSRT				
	No exclusions		Outlier exclusions			No exclusions		Outlier exclusions		
ROI	U	*p*	U	N	*p*	U	*p*	U	N	*p*
R STR	142	.044	128	27	.076	161	.045	131	28	.13
R GPe	154	.009*****	140	27	.017	172	.013	157	29	.023
R STN	88	.667	73	26	.595	94	.461	50	26	.085
RSN	99	<.999	84	25	.725	N/A	N/A	N/A	N/A	N/A
L STR	N/A	N/A	N/A	N/A	N/A	158	.061	129	28	.156
L STN	N/A	N/A	N/A	N/A	N/A	131	.461	101	27	.614
L SN	134	.104	120	27	.169	166	.026	151	29	.046

Note. Stop signal reaction time (**SSRT**) was estimated using the mean and integration methods. **ROI**= region of interest; **U=** Mann-Whitney U value; **N=**number of participants (without exclusions=28 for mean estimates and 30 for integration estimates); ***p***=*p*-value; **R**=right; **L**=left; **STR**=striatum; **GPe**=globus pallidus externa; **GPi**=globus pallidus interna; **STN**=subthalamic nucleus; **SN**=substantia nigra; **THAL**=thalamus; **N/A**= non-parametric test not required. *****Significant p-values did not survive correction for multiple comparisons (all exceed α=.0028).

APP10.2.1.1.3. Correlations between %BOLD and SSD and %BOLD pre- vs. post-50%SSD.

Correlation analyses were computed to establish the %BOLD in relation to the SSD in the SST. 6 delays (SSDs) were used for each behavioural run. As within-As within-subject data were highly correlated, separate analyses were conducted for each participant and each ROI separately. Here, non-parametric Spearman's rho was used for the correlation analyses. Resultant coefficients were then subjected to Frequentist one-sample t-tests to ascertain whether there was an effect of increasing delay between stimulus and signal.

Paired sample t-tests in relation to signal onset (pre-vs. post-50%SSD) are also reported.

Table APP10.2.4. One-sample t-tests of coefficients yielded from within-subject correlations across SSD and paired sample t-tests between %BOLD when stop signals were presented before or after the 50%SSD.

	Correlation SSD			Pre vs. post 50%SSD				
ROI	t	*p*	α	t	df	*p*	α	BF
R STR^{++}	0.96	.344		-0.35	27	.730		0.21
R GPe	1.41	.170		-1.46	27	.157		0.52
R GPi	0.27	.786		0.89	29	.383		0.28
R STN	1.4	.172		-1.06	29	.299		0.32
R SN	1.59	.122		-2.31	28	.028		1.92
R THAL	2.77	.010	.0029	-2.34	29	.024		2.19
L STR	0.9	.375		-0.48	27	.635		0.22
L GPe	1.64	.112		-1.37	29	.18		0.46
L GPi	0.89	.382		-1.73	29	.095		0.73
L STN^{++}	1.9	.067		**-3.22**	28	.003	.0033	**12.01**
L SN^{++}	2.23	.034		**-3.71**	26	.001	.0029	**34.47**
L THAL	2.84	.008		**-3.28**	29	.003	.0031	**13.81**

Note. **Correlation SSD**: as within-subject %BOLD across SSDs were highly correlated, separate correlations were conducted for each participant and each ROI. Resultant Pearson's coefficients were subjected to either Frequentist or Bayesian one-sample t-tests to ascertain whether there was an effect of increasing delay between stimulus and signal. **Pre- vs. post 50%SSD** refers to the results of paired sample t-tests when signals were presented before or after the 50%SSD. **ROI**=region of interest; **t=**t-value, significant t-values are reported in bold; ***p***=*p*-value; **α**= alpha-level; **BF**=Bayes Factor, BFs>3 are reported in bold; **R**=right; **L**=left; **STR**=striatum; **GPe**=globus pallidus externa; **GPi**=globus pallidus interna; **STN**=subthalamic nucleus; **SN**=substantia nigra; **THAL**=thalamus; $^{++}$=non-parametric required (pre vs. post analysis only). All degrees of freedom=29. Holm-Bonferonni correction was conducted across all ROIs including subcortical ROIs reported in Table APP10.1.3. α calculated as: $\alpha(k)=0.05/(n-k+1)$, where n is the number of ROIs (in this case 18), and k is the rank ordering of p-values from 1 to n.

Non-parametric Wilcoxon signed ranks tests conducted for analysis of %BOLD when signals were presented pre- vs. post 50%SSD.

RSTR: Z=.77, *p*=.441, N=30; RSTR outliers excluded: Z=0.84, *p*=.399, N=28.

LSTN: Z=2.4, *p*=.017, N=30; LSTN outliers excluded: Z=2.84, *p*=.004, N=29.

LSN: Z=2.42, *p*=.016, N=30; LSN outliers excluded: Z=3.15, *p*=.002, N=27.

APP10.2.1.2. Relationships between indices of non-inhibitory action updating and %BOLD

APP10.2.1.2.1. Correlations between %BOLD, DRT2 and the size of the decision bottleneck.

Table APP10.2.5. Correlations between %BOLD in subcortical ROIs acquired from the contrast double signal>double no-signal with DRT2 and estimated size of the PRP.

	DRT2					Size			
ROI	r	df	*p*	α	BF	r	df	*p*	BF
R STR	-0.11	27	.563		0.23	0.08	26	.704	0.22
R GPe	-0.21	26	.291		0.35	-0.23	25	.249	0.38
R GPi^{++}	0.01	26	.955		0.2	0.12	25	.568	0.24
R STN	-0.14	27	.455		0.25	0.09	25	.673	0.22
R SN	-0.4	26	.037	.0035	1.64	0.23	26	.235	0.39
R THAL	-0.34	25	.080		0.84	0.28	26	.155	0.54
L STR	-0.19	27	.325		0.31	0.03	26	.876	0.2
L GPe	-0.11	26	.571		0.23	0.12	26	.539	0.24
L GPi	-0.12	26	.539		0.24	-0.1	27	.595	0.22
L STN	-0.36	26	.063		1.07	-0.01	27	.947	0.2
L SN	-0.22	24	.286		0.36	0.16	26	.404	0.27
L THAL	-0.21	24	.310		0.34	0.36	26	.063	1.07

Note. **DRT2**=the latency of the non-inhibitory action updating process; **Size**=size of the PRP; **ROI**= region of interest; **r=** Pearson's correlation coefficient; ***p***=p-value; **α**=alpha level; **BF**=Bayes Factor; **R**=right; **L**=left; **STR**=striatum; **GPe**=globus pallidus externa; **GPi**=globus pallidus interna; **STN**=subthalamic nucleus; **SN**=substantia nigra; **THAL**=thalamus; $^{++}$= non-parametric required (for DRT2 analysis only)**.** Note that Holm-Bonferonni correction was conducted across all ROIs including subcortical ROIs reported in Table APP10.1.4. α calculated as: $\alpha(k)=0.05/(n-k+1)$, where n is the number of ROIs (in this case 16), and k is the rank ordering of p-values from 1 to n.

Non-parametric Spearman's rho was conducted for RGPi.

RGPi %BOLD and DRT2: With outliers. $rs_{(28)}=-0.01$, $p=.958$. Without outliers: $rs_{(26)}=-.03$, $p=.888$.

RGPi %BOLD and size of decision bottleneck: With outliers= $rs_{(28)}=0.08$, $p=.659$. without outliers. $rs_{(25)}=0.13$, $p=.530$.

APP10.2.1.2.2.Re-analysis of %BOLD with DRT2 and the size of the decision bottleneck

Table APP10.2.6. Differences in %BOLD in subcortical ROIs between participants with short vs. long DRT2s and small vs. large PRPs. Independent t-tests were conducted subsequent to median split of DRT2 and size of PRP.

	DRT2					Size			
ROI	t	df	*p*	α	BF	t	df	*p*	BF
R STR	1.75	28	.091		1.07	1.2	24	.905	0.37
R GPe	1.25	27	.223		0.62	1.28	25	.212	0.65
R GPi$^{++\lozenge}$	-0.4	27	.696		0.37	-0.72	25	.479	0.43
R STN	1.28	27	.211		0.64	-1.13	23	.27	0.59
R SN$^{\lozenge\lozenge}$	1.86	27	.074		1.24	-0.7	24	.489	0.44
R THAL	1.9	28	.069		1.29	-0.79	24	.437	0.46
L STR	1.89	28	.07		1.27	0.26	24	.8	0.37
L GPe	0.62	20.81	.541		0.4	0.54	25	.594	0.4
L GPi	0.09	26	.932		0.36	0.5	24	.623	0.4
L STN	2.49	27	.019	.0031	**3.14**	0.77	25	.451	0.45
L SN$^{\lozenge}$	1.21	26	.238		0.61	-0.05	24	.96	0.36
L THAL	1.23	28	.229		0.61	-1.08	24	.293	0.55

Note. **DRT2=** the latency of the non-inhibitory updating process; **Size=**size of the PRP. The size of the PRP for 3 participants was identical to the median and were excluded. **ROI**= region of interest; **t=** t-value; **df=**degrees of freedom (adjusted where Levene's test for homoscedasticity was significant); ***p***=p-value; **BF**=Bayes Factors, BF>3 shown in bold; **R**=right; **L**=left; **STR**=striatum; **GPe**=globus pallidus externa; **GPi**=globus pallidus interna; **STN**=subthalamic nucleus; **SN**=substantia nigra; **THAL**=thalamus**;** $^{+}$ and $^{\lozenge}$= analysis conducted on transformed data for DRT2 and size analysis, respectively; $^{\lozenge\lozenge}$=non-parametric required (size analysis only). Holm-Bonferonni correction was computed for all ROI analyses- including those reported in Table APP10.2.5. α calculated as: α(*k*)=0.05/(*n*-*k*+1), where *n* is the number of ROIs (in this case 16), and *k* is the rank ordering of *p*-values from 1 to *n.*

Non-parametric Mann-Whitney U conducted for RGPi and DRT2. With outliers:

Without outliers: U=102, *p*=.683, N=30. Without outliers: U=102, *p*=.914, N=29.

Non-parametric Mann-Whitney U conducted for RSN for size of bottleneck.

With outliers: U=82, *p*=.43, N=27. Without outliers: U=108, *p*=.231, N=26.

APP10.2.1.2.3. Correlations between %BOLD and SOA and %BOLD pre- vs. post- decision bottleneck.

Correlation analyses were computed to establish the %BOLD in relation to the SOA in the DT. 6 delays (SOAs) were used for each behavioural run. As within-As within-subject data were highly correlated, separate analyses were conducted for each participant and each ROI separately. Here, non-parametric Spearman's rho was used for the correlation analyses. Resultant coefficients were then subjected to Frequentist one-sample t-tests to ascertain whether there was an effect of increasing delay between stimulus and signal.

Paired sample t-tests in relation to signal onset (pre-vs. post decision bottleneck) are also reported.

Table APP10.2.7. One-sample t-tests of coefficients yielded from within-subject correlations across SOAs and paired sample t-tests between %BOLD when double signals were presented within or post PRP.

	Correlations		Pre vs. post			
ROI	t	*p*	t	df	*p*	BF
R STR^{++}	0.85	.404	-0.72	28	.48	0.25
R GPe	1.28	.21	-1.22	29	.232	0.38
R GPi	-0.98	.335	-0.22	29	.831	0.2
R STN^{++}	0.49	.628	-1.04	28	.309	0.32
R SN	0.96	.344	-1.94	28	.062	1.02
R THAL	1.34	.191	-0.92	28	.364	0.29
L STR^{++}	-0.43	.668	-0.7	28	.488	0.25
L GPe^{++}	0.56	.582	-0.9	27	.376	0.29
L GPi^{++}	0.46	.648	-0.21	28	.837	0.2
L STN	-0.36	.723	-0.64	29	.527	0.24
L SN^{++}	-0.7	.491	-1.46	28	.155	0.51
L THAL	1.85	.074	-1.77	29	.087	0.78

Note. **Correlation SOA**: as within-subject %BOLD across SOAs were highly correlated, separate correlations were conducted for each participant and each ROI. Resultant Spearman's coefficients were subjected to either Frequentist one-sample t-tests to ascertain whether there was an effect of increasing delay between stimulus and signal. Corresponding degrees of freedom=29. **Pre- vs. post** refers to the results of paired sample t-tests when signals were presented within or post-bottleneck. **ROI**=region of interest; **t=**t-value; ***p***=p-value; **BF**=Bayes Factor; **R**=right; **L**=left; **STR**=striatum; **GPe**=globus pallidus externa; **GPi**=globus pallidus interna; **STN**=subthalamic nucleus; **SN**=substantia nigra; **THAL**=thalamus; $^{++}$= non-parametric analysis required (pre vs. post analysis only). α-level not shown as all $p>.05$.

Table APP10.2.8. Non-parametric Wilcoxon signed ranks tests for within- vs. post PRP, with and without outlier exclusion.

	No exclusions			With exclusions		
ROI	Z	N	*p*	Z	N	*p*
R STR	0.59	30	.558	0.29	29	.770
R STN	1.13	30	.258	0.87	29	.387
L STR	0.63	30	.53	0.34	29	.738
L GPe	1.04	30	.299	0.48	28	.633
L GPi	-0.07	30	.943	-0.4	29	.689
L SN	1.57	30	.116	1.33	29	.184

Note. **ROI**= region of interest; **Z**= standardized score; **N**= number of participants; ***p***=p-value; **STR**=striatum; **GPe**=globus pallidus externa; **GPi**=globus pallidus interna; **STN**=subthalamic nucleus; **SN**=substantia nigra; **THAL**=thalamus.

APP10.2.1.3. Lateralization of action updating

Table APP10.2.9. Paired sample t-tests between right and left ROIs under inhibitory and non-inhibitory action updating conditions.

Contrast	ROI	Hemisphere	t	df	*p*	α	BF
Stop signal>	STR	Right	**6.42**	28	<.001	.0083	**28725**
stop no-signal	GPe^{+}	Right	1.23	26	.230		0.4
	GPi	Left	1.24	26	.227		0.41
	STN	Right	**2.75**	29	.01	.0125	**4.47**
	SN	Right	**2.58**	27	.016		**3.15**
	THAL	Right	**5.49**	28	<.001	.01	**2827**
Double-signal>	STR	Left	1.25	29	.221		0.4
double no-signal	GPe^{++}	Left	1.1	28	.281		0.34
	GPi	Left	1.6	29	.121		0.61
	STN	Left	0.45	29	.656		0.21
	SN	Left	2.24	27	.033	.0083	1.7
	THAL	Left	1.35	27	.190		0.45

Note. **ROI**= region of interest, **Hemisphere**=the hemisphere for which the corresponding ROI demonstrated the greatest %BOLD; **t**=t-value, significant t-values are reported in bold; ***p***=p-value; **α**= alpha level; **BF**=Bayes Factors, BFs>3 are reported in bold; **STR**=striatum; **GPe**=globus pallidus externa; **GPi**=globus pallidus interna; **STN**=subthalamic nucleus; **SN**=substantia nigra; **THAL**=thalamus; $^{+}$ = analysis conducted on transformed data; $^{++}$ = non-parametric analysis required. Holm-Bonferonni correction was computed for all ROI analyses- including those reported in Table APP10.1.8. α calculated as: $\alpha(k)=0.05/(n-k+1)$, where n is the number of ROIs (in this case 8), and k is the rank ordering of p-values from 1 to n.

Non-parametric Wilcoxon signed ranks test for the GPe in the DT (double signal>double no-signal).

With outliers: Z=1.72, N=30, *p*=.086; without outliers: Z=1.48, N=29, *p*=.139.

10.3. Appendices for Chapter 4.

APP10.3.1. Additional screening form for female participants

Magnetic Resonance Spectroscopy: Additional screening

As part of the current study we are interested in the neurotransmitter Gamma-Aminobutyric Acid (GABA). Previous studies have found GABA concentrations to fluctuate across the menstrual cycle. As such, we *may* need to arrange testing sessions to fall within specific weeks of your individual cycle. Please read the following information carefully. If you agree to the statements provided and are happy for us to use this information then please complete this form and add your signature. You are under no pressure to complete all questions or to give your consent. You are free to withdraw from the study at any time.

By completing this form you are agreeing to the following:

- I understand that information regarding my menstrual cycle will be used as part of the study.
- I understand that my anonymised data may be made publically available as part of the 'open science' initiative (see the Information Sheet for further details).

We would be grateful if you could please complete this form as accurately as possible.

If you have any questions regarding the open science initiative or any other aspect of this questionnaire please ask the person who gave you this form.

1) **Do you consider your menstrual cycles to occur regularly?**

☐ Yes ☐ No

If you answered no, could you please provide more details (e.g. do your cycles vary in duration, are periods sometimes absent, etc.).

_____

_____

_____

2) **What is the average duration of your menstrual cycle? Here, please consider the duration of one cycle as the time in days between the first day of your period in month A and the first day of your period in the following month, B.** e.g. if the first day of your period in January was on the 2nd and the first day of your next period was on February 2nd your cycle would be 31 days.

_____

3) **Are you currently taking any form of hormone-based contraception?**

☐ Yes ☐ No

If you answered <u>yes</u>, could you please provide details:

_____

If you answered <u>no</u>, could you please confirm the date of the first day of your last period?

_____

Name: _____

Signature: _____

Date: _____

APP10.3.2. Group level exclusion criteria based on behavioural performance in the sham cTBS session.

Participants were not provided feedback during testing sessions to prevent modulation of responses for reasons other than the intervention employed. However, criteria were set prior to data collection for potential exclusions after testing based on behavioural performance at baseline. Although no participants were excluded, they are reported here for completion:

13. If successful performance on stop signal trials across a testing session was greater than 75%. This would indicate that either i) the participant had engaged in proactive slowing strategy in order to increase successful inhibition or ii) the ineffectiveness of the psychophysical inhibition function(s) to maintain ~50% successful stopping.

14. At the group level, if no-signal RTs were more than 3 standard deviations from the mean as these participants would be deemed slow responders; measured for each context separately in the *sham* condition only. No-signal RTs will be considered regardless of arrow directionality.

APP10.3.3. Justification for use of MRS

MRS is a technique that enables the detection of radiofrequency signals of hydrogen spins that vary between neurochemicals. Differences between different chemical species arise due to due to differences in the electron shielding caused by the structure of the molecule (Waddell et al. 2007; (Ke, Cohen, Bang, Yang, & Renshaw, 2000; Puts & Edden, 2012; Mullins et al., 2014). This results in a shift of spin resonance frequencies of the various neurochemicals relative to each other (chemical shift), yielding a spectrum in which different neurochemicals can be separated. This spectrum is plotted against chemical shift for which the scale is expressed in parts per million of the resonance frequency (ppm, Figure APP10.3.1). The area of peaks within spectra is representative of the signal produced by hydrogen atoms after application of a radiofrequency pulse and is approximately equivalent to the concentration of the neurochemical present (Puts & Edden, 2012).

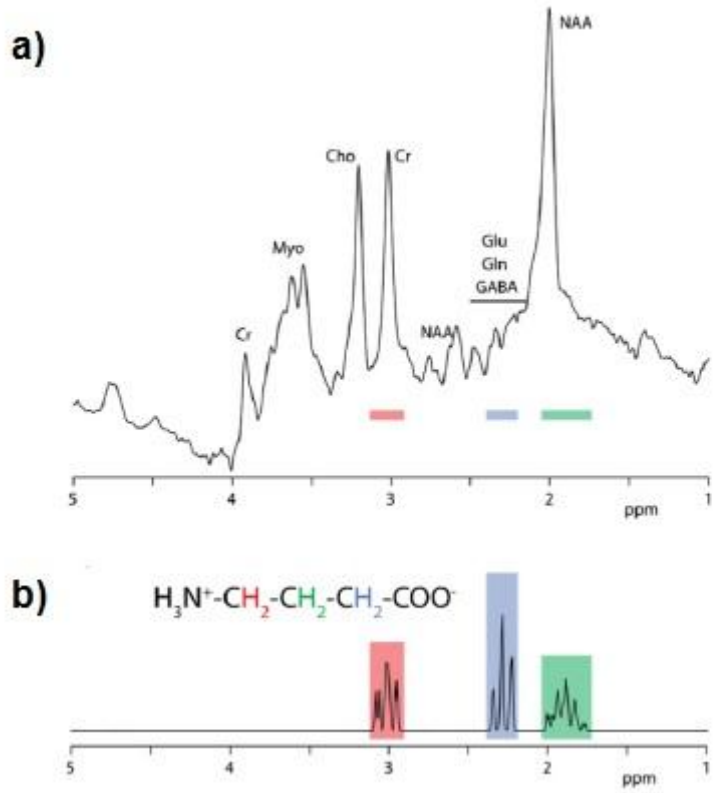


Figure APP10.3.1. An example of chemical shift data acquired via Magnetic Resonance Spectroscopy at 3 Tesla from (Puts & Edden, 2012). The chemical shift for all metabolites is presented in panel a, whereas panel b illustrates the presence of GABA multiplets caused by the presence of the methylene (CH_2) groups at 3 parts per million (ppm; pink), 2.3ppm (blue) and 1.5ppm (green) along the chemical shift axis. **Cr**=creatine, **Myo**=Myoinositol, **Cho**=choline, **NAA**=N-acetyl aspartate, **Glu**=glutamate, **Gln**=glutamine, **GABA=** γ-Aminobutyric Acid.

The presence of J-coupling (an interaction between neighbouring spins within the same molecule) can give rise to multiplets in the radiofrequency signals produced by different metabolites (Waddell et al. 2007). In particular, the presence of three methylene (CH_2) groups in the GABA molecule ($H_3N^+CH_2CH_2CH_2C00^-$) essentially splits the GABA signal into three, with peaks observed at 1.5ppm, 2.3ppm and 3ppm. This 'splitting' of the signal effectively reduces the amplitude of the individual peaks produced by the GABA molecule (although the area remains the same), which is already low relative to other metabolites (Mullins et al. 2014; Figure APP10.3.2b). This, in addition to overlaps in peaks between GABA and other metabolites along the chemical shift axis (Figure APP10.3.1a) makes the quantification of GABA problematic. Editing techniques can be used to minimise the influence of signal overlap and enable GABA quantification (Puts & Edden, 2012; Mullins et al. 2014; Mikkelsen, Singh, Sumner, & Evans, 2015). Here, I employ MEGA-PRESS, one of the most

commonly used editing techniques (see Section 4.3.3.3.4.4). Essentially, this protocol applies frequency selective pulses at 1.9ppm which has a 'knock-on' effect to the GABA peak produced at 3ppm due to the J-coupling between them. Subtraction of spectra with frequency selective pulses from those without enables the quantification of GABA at 3ppm (Figure APP10.3.2, Mullins et al. 2014). This effectively filters the spectrum, removing the majority of other chemical from the spectrum allowing clearer quantification of GABA.

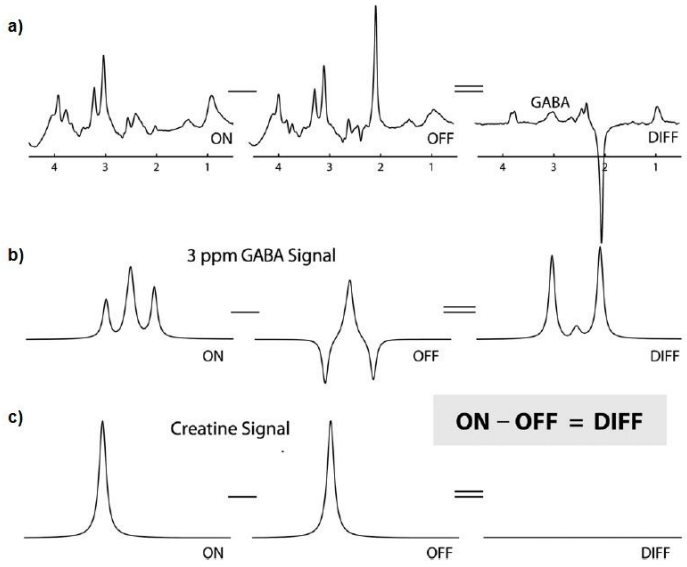


Figure APP10.3.2. Schematic of MEGA-PRESS editing used for GABA from Mullins et al. (2014). Panel a illustrates the subtraction of spectra without a frequency selective pulse (OFF) from spectra with a frequency selective pulse applied at 1.9ppm (ON). Panel b focuses on this subtraction on the GABA peak at 3ppm only and demonstrates the change in shape induced by the frequency selective pulse applied at 1.9ppm (ON). It can be see that the application of the frequency selective pulse has no effect on the signal produced by Creatine and thus it is essential removed by the subtraction of the OFF spectra from the ON spectra.

APP10.3.4. Justification for the use of Creatine as an internal reference

Although water is the most commonly used reference for GABA quantification (de Graaf, 2007), I chose to use Creatine (Cr) here. Cr has the advantage of being acquired at the same time as GABA, while water reference scans were acquired after the GABA acquisition. Using a Cr reference acquired simultaneously with the GABA measurement ensured that any temporal effects of cTBS that may potentially influence reference concentration occurred at the same time as GABA itself. Alternative simultaneously acquired metabolites have been used a references, such as N-acetyl aspartate (NAA), in

a number of other cTBS-GABA related papers (e.g. Stagg et al. 2009), but Cr has the advantage of its peak arising at 3.01ppm and thus is not effected by chemical shift displacement artefacts (the peak of NAA occurs at 2ppm, Figure APP10.3.2a; de Graaf, 2007). Furthermore, Cr has found to be a relatively stable and reproducible relative to water (Puts and Edden, 2012) and its concentration appears to remain unaffected by cTBS (Stagg *et al*., 2009).

APP10.3.5. Individual subject cTBS parameters and MNI co-ordinates

Table APP10.3.1. Individual subject MNI-coordinates and cTBS parameters for application to the rIFG.

P number	Target	Actual	% AdjMT	MNI
1	42	36	69	58, 12, 4
2	48	42	70	62, 12, 4
3	41	34	66	60, 16, 0
4	51	38	60	58, 18, 2
5	48	37	62	62, 10, 0
6	45	35	62	60, 12, 8
7	55	44	64	60, 16, 2
8	47	38	65	60, 14, 8
9	62	47	61	62, 10, 10
10	40	31	62	58, 20, 2
11	37	34	74	60, 18, 4
12	34	31	73	62, 12, 6
13	38	33	69	56, 14, 6
14	47	35	60	60, 16, 6
15	38	32	67	60, 14, 6
16	37	30	65	62, 8, 12
17	36	32	71	62, 14, 6
18	43	32	60	60, 10, 4
19	50	37	60	60, 14, 10
20	52	45	69	58, 20, 10
21	39	30	62	58, 14, 2
22	42	36	69	62, 14, 8
23	43	34	63	60, 16, 2
24	49	37	60	58, 18, 4
25	44	37	67	56, 14, 4
26	47	36	61	60, 12, 8
27	43	37	69	60, 10, 12
28	43	33	61	62, 8, 16
29	44	35	64	60, 10, 12
30	42	39	74	66, 0, 8

Note. **P number**= participant numberl **Target**= target TMS intensity (as % stimulator output); **Actual**=actual TMS intensity (as % stimulator output); **%AdjMT**= % of distance adjusted motor threshold intensity applied; **MNI**= rIFG coordinates in MNI standard space.

APP10.3.6. Results

All data were analysed both with and without outlier exclusion. Results in the main text are inclusive of outliers. Findings reported here are results subsequent to outlier exclusion. Non-paramterics, where required are also reported.

APP10.3.6.1 Baseline results

No-signal RT data were compared between the SST and DT. They were found to be prolonged in the SST relative to the DT ($t_{(27)}$=2.64, p=.013, BF=3.58). Non-parametric test result required. Prior to outlier exclusions: Z=2.64, p=.008, N=30. Subsequent to outlier exclusion: Z=2.25, p=.024, N=28.

Repeated measures ANOVA of DRT2 across short, intercept and long SOAs subsequent to outlier exclusion: $F_{(1.26,35.18)}$=164.09, p<.001, BF=143^{e+23}, where DRT2 at the shortest SOA was longer than DRT2 at the intercept ($p_{.0167}$<.001, BF=1.86^{e+14}) and at the longest SOA ($p_{.025}$<.001, BF=2.43^{e+9}). There was no difference between DRT2 at the intercept or longest SOA (p=.357, BF=0.29).

APP10.3.6.2. The effects of cTBS applied to the rIFG.

The onset times of each MRS/fMRI run were assessed to establish whether there were any differences between the active and sham sessions. Non-parametric tests required (Run 1: Z=1.57, p=.116; Run 2: Z=0, p<.999; Run 3: Z= -.18, p=.859 Run 4: Z=-.42, p=.673; N=30 for all analyses).

The overlap between pre- and post- cTBS voxels was found to be greater under sham relative to active conditions subsequent to outlier removal ($t_{(27)}$=2.29, $p_{.05}$=.03, BF=1.86). Non-parametric tests required. Sham overlap was also found to be greater than active overlap. Wilcoxon signed-ranks test prior to outlier exclusion: Z=1.96, p=.049, N=30. Subsequent to outlier exclusion: Z=2.16, p=.031, N=28.

Non-parametric analysis required to assess stop-signal accuracy. Accuracy was greater under sham vs. active cTBS conditions, but not significantly so (Z=0.93, p=.353, BF=0.35).

Table APP10.3.2. Paired sample t-tests for each dependent measure acquired in the active vs. sham testing sessions.

DV	t	df	*p*	BF
% SNS	-0.14	28	.888	0.2
% SS	-1.12	28	.271	0.38
SNS RT	-1.11	27	.278	0.2
DNS RT	-0.6	28	.556	0.2
SSRT	0.6	28	.553	0.37
DRT1	-0.42	28	.68	0.2
DRT2^{+}	-0.61	27	.549	0.21
GABA^{+}	2.01	28	.054	1.36
BOLD (Stop)	-0.28	28	.783	0.21

Note. **DV**= dependent variable; **t**=t-value; ***p***=*p*-value; **BF**=Bayes Factor; **SNS**= stop no-signal trials; **DNS**= double no-signal trials; **SS**= stop signal trials; **DS**= double signal trials; **RT**= reaction time; **SSRT**= stop signal reaction; **DRT1=**reaction time of the initial response on double signal trials; **DRT2**= reaction time of the additional response on double signal trials minus the signal onset asynchrony; **BOLD**= blood oxygen level dependent signal change in the right Inferior Frontal Gyrus. BOLD was extracted from signal>no-signal contrasts in either the SST or DT. $^{+}$= analysis conducted on transformed data. α-level not shown as all *p*>.05

Paired sample t-test between the size of the PRP under active vs. sham cTBS conditions revealed no difference subsequent to outlier removal: $t_{(28)}$=.87, *p*=.394, BF=0.28.

APP10.3.6.3. The relationship between dependent variables

Table APP10.3.3. Pearson's correlations between *baseline* measures of GABA concentration, %BOLD and behavioural measures of action updating.

DVs		r	df	*p*	α	BF
GABA	SNS RT	-0.24	27	.211		0.53
	DNS RT	-0.09	27	.64		0.29
	SSRT	-0.3	27	.121		0.8
	DRT1	-0.18	26	.35		0.39
	DRT2	0.26	26	.181		0.59
	BOLD (Stop)	-0.28	25	.152		0.65
	BOLD (Stop Fix)	-0.16	26	.41		0.36
	BOLD (Doub)	-.01	26	.98		0.27
	BOLD (Doub Fix)	0.22	27	.262		0.47
%BOLD (Stop)	SNS RT	-0.39	26	.04	.0036	1.47
	SSRT	0.05	25	.809		0.21
%BOLD (Double)	DNS RT	-0.29	26	.393		0.58
	DRT1	0.17	26	.393		0.29
	DRT2	0.04	27	.838		0.2

Note. **DVs**= dependent variables; **r**=Pearson's correlation coefficient;**df**= degrees of freedom; **p**=p-value; **BF**=Bayes Factor; **SNS RT**= reaction time to stop no-signal trials; **DNS RT**= reaction time to double no-signal trials; **SSRT**= stop signal reaction time; **DRT1=**reaction time of the initial response on double signal trials; **DRT2**= reaction time of the additional response on double signal trials minus the signal onset asynchrony; **%BOLD**= blood oxygen level dependent signal change in the rIFG. %BOLD was extracted from signal>no-signal contrasts in either the SST or DT or from signal>all fixations (**fix**) in either the SST or DT. Note that for any BFs calculated for GABA-related data the prior scale factor was reduced by √2 (see section 4.4.2) α calculated as: α(*k*)=0.05/(*n*-*k*+1), where *n* is the number of ROIs (in this case 14), and *k* is the rank ordering of *p*-values from 1 to *n.*

Table APP10.3.4. Correlations between *cTBS-induced* changes of GABA concentration, %BOLD and behavioural measures of action updating.

DVs		r	df	*p*	BF
GABA^{+}	SNS RT	-0.26	26	.895	0.59
	DNS RT	0.19	27	.336	0.41
	SSRT	0.02	25	.929	0.28
	DRT1	-0.03	27	.873	0.27
	DRT2^{++}	-0.2	26	.31	0.42
	BOLD (Stop)	0.27	25	.171	0.61
	BOLD (Stop Fix)	0.1	24	.629	0.31
	BOLD (Doub)	-0.06	25	.751	0.28
	BOLD (Doub Fix)	0.04	28	.822	0.27
%BOLD (Stop)	SNS RT	-0.06	25	.761	0.21
	SSRT	-0.07	26	.738	0.21
%BOLD (Double)	DNS RT	0.06	26	.767	0.21
	DRT1	0.09	26	.662	0.22
	DRT2^{++}	-0.06	27	.973	0.21

Note. **DVs**= dependent variables, **r**=Pearson's correlation coefficient; **df**=degrees of freedom; ***p***=*p*-value; **BF**=Bayes Factor; **SNS RT**= reaction time to stop no-signal trials; **DNS RT**= reaction time to double no-signal trials; **SSRT**= stop signal reaction time; **DRT1=**reaction time of the initial response on double signal trials; **DRT2**= reaction time of the additional response on double signal trials minus the signal onset asynchrony; **%BOLD**= blood oxygen level dependent signal change in the rIFG. %BOLD was extracted from signal>no-signal contrasts in either the SST or the DT or from signal>all fixations (**fix**) in either the SST or DT. Note that for any BFs calculated for GABA-related data the prior scale factor was reduced by √2 (see section 4.4.2). $^{+}$= analysis conducted on transformed data; $^{++}$= non-parametric required. α level for Holm-Bonferonni comparison not shown as all *p*>.05.

Non-paramateric correlations required for cTBS induced difference scores involving DRT2.

DRT2 and GABA concentration. With outliers: $rs_{(28)}$=-0.18, *p*=.347. Without outliers: $rs_{(26)}$=-0.14, *p*=.489

DRT2 and %BOLD (Double). With outliers: $rs_{(28)}$=0.06, *p*=.766. Without outliers: $rs_{(27)}$= -0.002, *p*=.992

APP10.3.6.4. Test re-test reliability and variability of GABA quantification

Frontal GABA has proven difficult to quantify in some studies due to inhomogeneity in the magnetic field towards the front of the head (de Graaf, 2007). As such I explored the variability of GABA both within and between subjects for the sham-related data. Variability can be used to describe the distribution of data around the mean (Shrout &

Fleiss, 1979; Vaz, Falkmer, Passmore *et al.*, 2013) and was measured via intra-class correlation coefficients (ICCs) to provide a dimensionless indication of measurement variability. Separate 2-way random effects models for absolute agreement were used and standard errors of measurement (SEM) were computed for each ICC where: $SEM = SD\sqrt{(1 - ICC)}$.

Within and between coefficients of variation (CV_{wp} and CV_{bp}, respectively) were calculated in accord with the procedure outlined in Mikkelsen, Singh, Sumner, & Evans (2015) as detail below.

15. CVs were computed separately for each participant using:

    $CV = 100(\frac{\sigma p}{\mu p})$, where σp = standard deviation, and μp = the mean, of measures for a participant.

16. CV_{wp} was computed as:

    $p = \overline{CVp}$, where $\overline{CVp}$ = the mean of all CVp values across participants.

17. CV_{bp} was computed as:

    $p = 100(\frac{\sigma(\mu p)}{\mu})$, where $\sigma(\mu p)$ = standard deviation of participant means and μ = mean of participant means.

APP10.3.6.5. Exploratory analyses

APP10.3.6.5.1. Exploration of cTBS over time

Table APP10.3.5. Repeated measures ANOVA as applied to each dependent variable, with cTBS (active vs. sham) and time (number of runs) as factors.

DV	Effect	F	df	*p*	BF
GABA^{++}	cTBS	1.99	(1,15)	.179	0.5
	Time	1.51	(1,15)	.238	0.43
	Interac	0.11	(1,15)	.748	0.33
BOLD (stop) $^{++}$	cTBS	1.26	(1,22)	.274	0.45
	Time	0.76	(1,22)	.392	0.27
	Interac	0.24	(1,22)	.628	0.34
BOLD (double)$^{++}$	cTBS	0.05	(1,27)	.828	0.2
	Time	2.52	(1,27)	.123	0.5
	Interac	1.66	(1,27)	.208	0.71
SSRT	cTBS	0.29	(1,27)	.596	0.17
	Time	**36.21**	(2.35,63.37)	<.001	**7.68^{e+15}**
	Interac	0.67	(2.03,54.81)	.516	0.08
DRT2	cTBS	0.09	(1,26)	.766	0.16
	Time	**6.59**	(2.03,52.96)	.003	**50.12**
	Interac	0.18	(3,78)	.907	1.49
SNS RT	cTBS	.001	(1,26)	.974	0.16
	Time	**7.06**	(3,78)	<.001	**6.47**
	Interac	1.46	(3,78)	.233	0.1

Note. **DV**= dependent variable; **Effect**=refers to either main effects of cTBS or time or interaction effects (**Interac**); **F**=F-value, significant F-values are reported in bold; **df**=degrees of freedom (Greenhouse-Geisser corrected where applicable); ***p***=p-value; **BF**=Bayes Factor, BFs>3 are reported in bold; **GABA**= GABA concentration; **BOLD**= blood oxygen level dependent % signal change; **RT**= reaction time; **stop**= stop signal>stop no-signal; **double**= double signal>double no-signal; **SSRT**= stop-signal RT; **DRT2**= RT between onset of additional response and onset of signal in the DT; **DRT1**= reaction time of the initial response on double-signal trials; **SNS**= stop no-signal trials; **DNS**= double no-signal trials; $^{++}$= non-parametric analyses required.

Table APP.10.3.6. Pairwise comparisons between behavioural dependent variables and run number.

DV	Comparison	*p*	α	BF
SSRT	1<2	**<.001**	.0125	**1947.38**
	1<3	**<.001**	.01	**388576.51**
	1<4	**<.001**	.0083	**522722.67**
	2<3	**<.001**	.0167	**797**
	2<4	.003	.025	**13.25**
	3>4	.601		0.23
DRT2	1<2	**.016**	.0125	**3.16**
	1<3	**.001**	.0083	**57.78**
	1<4	**.**089		0.8
	2<3	.029		1.91
	2<4	.71		0.22
	3>4	**.006**	.01	**7.33**
SNS RT	1<2	.015	.0125	**3.33**
	1<3	**<.001**	.0083	**57.94**
	1<4	**.**025		2.16
	2<3	.012		**3.9**
	2<4	.447		0.27
	3>4	.08		0.87

Note. Pairwise comparisons conducted for behavioural dependent variables only as no main effect of run number was found for GABA or %BOLD measures (see Table 4.8). **DV**= dependent variable; **Comparison**=run numbers compared (the run for which the DV was greater is indicated); ***p***=*p*-value, significant *p*-values are reported in bold; **BF**=Bayes Factor, BFs>3 are reported in bold; **SSRT=**stop-signal reaction time; **DRT2**=the duration between the onset of the additional response and the signal onset on double-signal trials; α calculated as: α(*k*)=0.05/(*n*-*k*+1), where *n* is the number of comparisons (in this case 6), and *k* is the rank ordering of *p*-values from 1 to *n.* Correction was conducted separately for each DV.

Friedman's tests for GABA and BOLD data with cTBS (active vs. sham) and time (time 1 vs. time 2) as factors.

GABA with outliers: $X^2_{(3)}$=2.82, *p*=.42, N=20. With outliers excluded: $X^2_{(3)}$=2.17, *p*=.538, N=16.

BOLD (stop) with outliers: $X^2_{(3)}$=1.61, *p*=.798, N=29. With outliers excluded: $X^2_{(3)}$=1.28, *p*=.734, N=23.

BOLD (double) with outliers: $X^2_{(3)}$=4.74, *p*=.192, N=29. With outliers excluded: $X^2_{(3)}$=3.99, *p*=.734, N=28.

APP10.3.6.5.2 Linear mixed effects analyses to explore the effect of cTBS over time

As this study provided an opportunity to provide a partial replication of Verbruggen et al.'s (2010) findings, I further explored the effects of cTBS on behaviour using linear

mixed effects (LMEs). Such analysis techniques are advantageous in circumstances where data is correlated (such as repeated measures over time) and enable explicit modelling of both fixed and random effects (Pinheiro & Bates, 2000; West, Walsh & Galeki, 2007). Fixed effects typically refer to the parameter of interest (the predictor or explanatory variable), such as the mode of cTBS application here (i.e. active or sham). Conversely, random effects are those effects that cannot be controlled experimentally, such as subject-specific variation. The inclusion of random effects acts to reduce the error present in the model (Pinheiro & Bates, 2000). Here, separate LMEs were computed for behavioural measures of interest (i.e. SSRT, DRT2 and no-signal RTs in the stop and double contexts). As per Verbruggen et al. (2010) a moving window approach was used for behavioural analyses. Here, DVs were calculated separately for active and sham sessions for every 6 blocks (corresponding to 36 signal trials per window) providing a total of 19 separate windows per session (i.e. window 1= blocks 1-6, window 2= blocks 2-7...window 3= blocks 19-24)[129] per subject.

As per Verbruggen et al. (2010), I adopted a top-down model building strategy, where the most parsimonious model that best predicted the measure of interest was selected. Bayesian equivalents were computed throughout using either the JZS prior or the effect sizes as per Verbruggen et al. (2010)[130]. Models were computed both with and without outliers. Note, that outlier exclusion had no influence on the final model fits for any of the dependent variables. Results are reported with outliers included. Specific steps are in accord with Verbeke & Molengberghs' (2000) suggestions and are outlined in Figure APP10.3.3. All analyses pertaining to each dependent measure are outlined below. For each test the log-likelihood (LL), degrees of freedom (df), X^2 and *p*-value are reported.

[129] Note that run 3 data in the Sham condition was corrupt for 1 participant. Although Frequentist approach to LMEs are able to cope with missing data sets, this not the case for Bayesian alternatives- as such data for this participant was excluded from these analyses.

[130] Effect sizes were only explicitly reported for SSRT, DRT2 and DRT1 in Verbruggen et al. (2010).

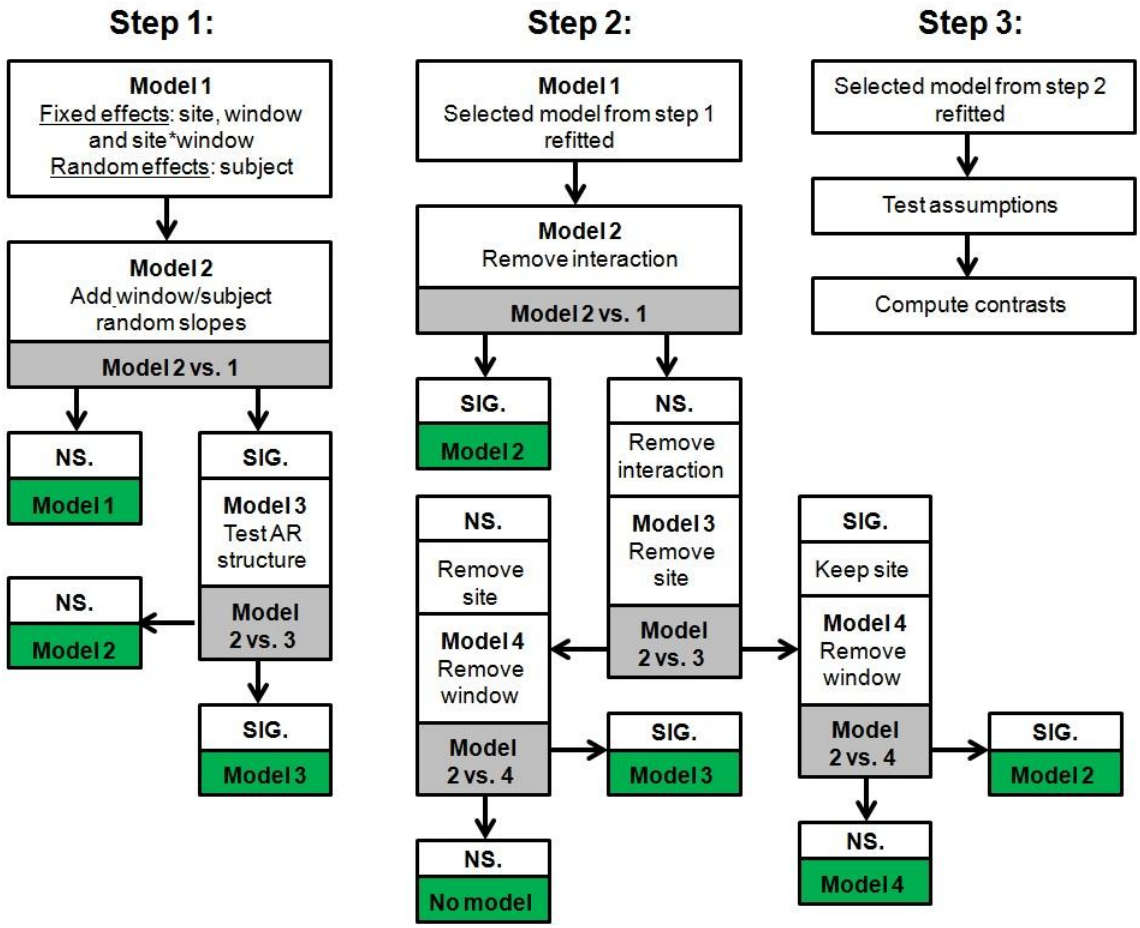


Figure APP10.3.3. Schematic of the steps required to fit linear mixed effects models to the data. In Step 1, all fixed effects and potential interactions were added to the model. Here, site of cTBS application and run number were added to the model as fixed effects and subject added as random effect (Model 1). Initial model fit was established via Restricted Maximum Likelihood (REML) estimation to provide an unbiased estimate of the covariance parameters associated with random effects. In accord with West *et al*. (2007) I did not test whether subject specific effects provided a better model fit than the inclusion of fixed effects only as subject-specific variation is implied in the experimental design. In Model 2, random slopes for each participant were added to allow for different slopes to be added for each subject[131]. The autoregressive (AR) structure of the residuals was then ascertained (Model 3). In Step 2 the selected model from Step 1 was re-fit using Maximum Likelihood estimation (REML is not appropriate to test fixed effects; West et al. 2007). The aim of Step 2 was to reduce the model. Initially the interaction effect was removed to assess the effect on the model, followed by the main effects of site and window. All model fits were with X^2 likelihood ratios to obtain an objective measure of significance (Field, 2013) and compared to determine the selected model at each stage. The selected model (green) is outlined for each step depending on whether the result of the X^2 likelihood test was significant (SIG.) or non-significant (NS.).

[131] Note that the addition of window as a random slope to the model meant that resultant p-values had to be adjusted to account for the mixture of X^2 distributions used to test the null hypothesis (such mixtures of distributions only need to be accounted for when covariates are included as parameters as opposed to correlational parameters only; Pinheiro & Bates, 2000).

APP10.3.6.5.2.1. SSRT: For these analyses, only window was found to significantly contribute to the model fit. SSRT was found to increase steadily across windows in both the active and sham sessions (Figure APP10.3.4).

Step 1: Determine the random structure and covariance structure

Model	Test	Random	Covariance	LL	df	X^2	*p*
1	Initial REML	1		2371.93	6		
2	Random window 1 vs. 2	1 + window		2421.58	8	$X^2_{(1.5)}$=99	<.001
3	Random window 2 vs. 3	1 + window	AR	3150.82	9	$X^2_{(1)}$=1458.47	<.001

Decision test model 2: add random window; decision test model 3; use autoregressive (AR) structure

Step 2: Determine fixed effects

Model	Test	Fixed	LL	df	X^2	*p*
1	Initial ML	site x window	2729.48	9		
2	Remove interaction 1 vs. 3	site + window	2729.37	8	$X^2_{(1)}$=0.56	.456
3	Remove site 2 vs. 3	window	2729.37	7	$X^2_{(1)}$=0.02	.879
4	Remove window 2 vs. 4	site	2702.09	7	$X^2_{(1)}$=59.48	<.001

Decision test model 2: remove interaction; decision tests model 3: remove site; decision test model 4: keep window

Step 3: Test final model

Effects	F			*p*
Window	F(1,1072)=349.76			<.001
Contrasts	B	SE(B)	t	*p*
Intercept	222.79	6.81	32.7	<.001
Window	2.43	0.13	18.7	<.001

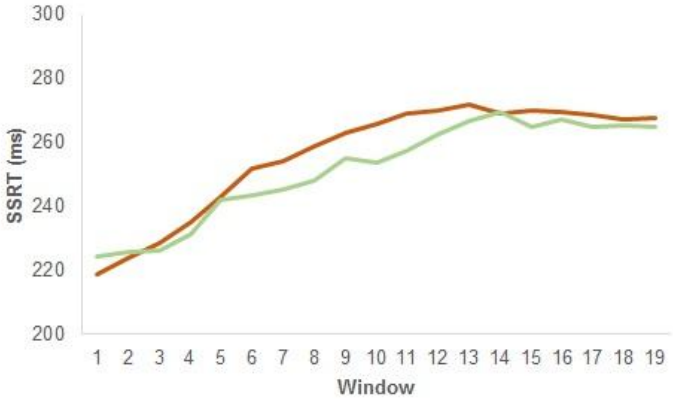


Figure APP10.3.4. The change in stop signal reaction time (SSRT) across windows in the active (orange) and sham (green) conditions.

APP10.3.6.5.2.2. DRT2: Only window was found to contribute significantly to model fits. DRT2 was found to steadily increase across windows in both the active and sham sessions (Figure APP10.3.5)

Step 1: Determine the random structure and covariance structure

Model	Test	Random	Covariance	LL	df	X^2	*p*
1	Initial REML	1		2218.3	6		
2	Random window 1 vs. 2	1 + window		2299.45	8	$X^2_{(1.5)}$=162.3	<.001
3	Random window 2 vs. 3	1 + window	AR	3067.07	9	$X^2_{(1)}$=1535.23	<.001

Decision test model 2: add random window; decision test model 3; use autoregressive (AR) structure

Step 2: Determine fixed effects

Model	Test	Fixed	LL	df	X^2	*p*
1	Initial ML	site x window	3089.02	9		
2	Remove interaction 1 vs. 3	site + window	3089.02	8	$X^2_{(1)}=1.3^{e-08}$	.997
3	Remove site 2 vs. 3	window	3088.9	7	$X^2_{(1)}$=0.24	.624
4	Remove window 2 vs. 4	site	3084.71	7	$X^2_{(1)}$=8.62	.003

Decision test model 2: remove interaction; decision tests model 3: remove site; decision test model 4: keep window

Step 3: Test final model

Effects	F			*p*
Window	F(1,1072)=40.37			<.001
Contrasts	B	SE(B)	t	*p*
Intercept	538.51	9.4	57.33	<.001
Window	0.88	0.14	6.35	<.001

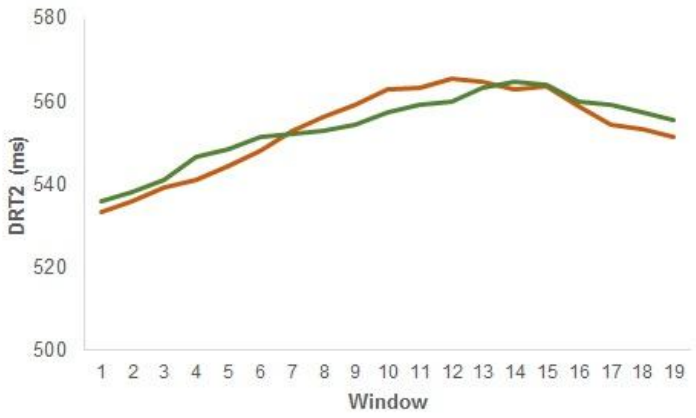


Figure APP10.3.5. The change in the latency of the additional response on double signal trials (DRT2) across windows in the active (orange) and sham (green) conditions.

APP10.3.6.5.2.3. DRT1: Only window was found to contribute significantly to model fit. DRT1 was found to steadily increase across windows in both the active and sham sessions (Figure APP10.3.6)

Step 1: Determine the random structure and covariance structure

Model	Test	Random	Covariance	LL	df	X^2	*p*
1	Initial REML	1		2546.27	6		
2	Random window 1 vs. 2	1 + window		2582.86	8	$X^2_{(1.5)}$=73.18	<.001
3	Random window 2 vs. 3	1 + window	AR	3335.15	9	$X^2_{(1)}$=1504.58	<.001

Decision test model 2: add random window; decision test model 3; use autoregressive (AR) structure

Step 2: Determine fixed effects

Model	Test	Fixed	LL	df	X^2	*p*
1	Initial ML	site x window	3358.39	9		
2	Remove interaction 1 vs. 3	site + window	3358.03	8	$X^2_{(1)}$=0.72	.38
3	Remove site 2 vs. 3	window	3357.89	7	$X^2_{(1)}$=0.28	.596
4	Remove window 2 vs. 4	site	3353.52	7	$X^2_{(1)}$=9.02	.003

Decision test model 2: remove interaction; decision tests model 3: remove site; decision test model 4: keep window

Step 3: Test final model

Effects	F			*p*
Window	F(1,1098)=31.44			<.001
Contrasts	B	SE(B)	t	*p*
Intercept	446.17	5.64	79.13	<.001
Window	0.65	0.11	5.61	<.001

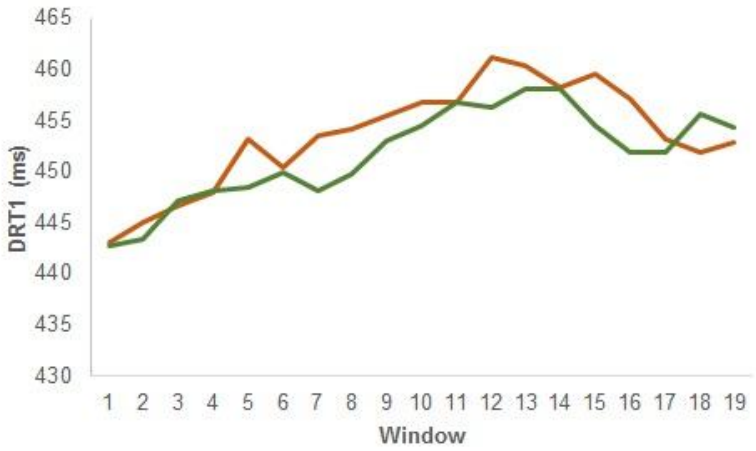


Figure APP10.3.6. The change in the latency of the initial response on double-signal trials (DRT1) across windows in the active (orange) and sham (green) conditions.

APP10.3.6.5.2.4. Stop no-signal RT: Neither window or cTBS was found to influence the latency of the reaction time to no-signal trials in the stop context (Figure APP10.3.7).

Step 1: Determine the random structure and covariance structure

Model	Test	Random	Covariance	LL	df	X^2	*p*
1	Initial REML	1		2547.38	6		
2	Random window 1 vs. 2	1 + window		2592.96	8	$X^2_{(1.5)}$=91.18	<.001
3	Random window 2 vs. 3	1 + window	AR	3683.27	9	$X^2_{(1)}$=2180.61	<.001

Decision test model 2: add random window; decision test model 3; use autoregressive (AR) structure

Step 2: Determine fixed effects

Model	Test	Fixed	LL	df	X^2	*p*
1	Initial ML	site x window	3705.43	9		
2	Remove interaction 1 vs. 3	site + window	3704.57	8	$X^2_{(1)}$=1.73	.188
3	Remove site 2 vs. 3	window	3704.11	7	$X^2_{(1)}$=0.92	.339
4	Remove window 2 vs. 4	site	3702.85	7	$X^2_{(1)}$=3.43	.065

Decision test model 2: remove interaction; decision tests model 3: remove site; decision test model 4: remove window

No further analyses conducted as no fixed effects contributed significantly to the model fit.

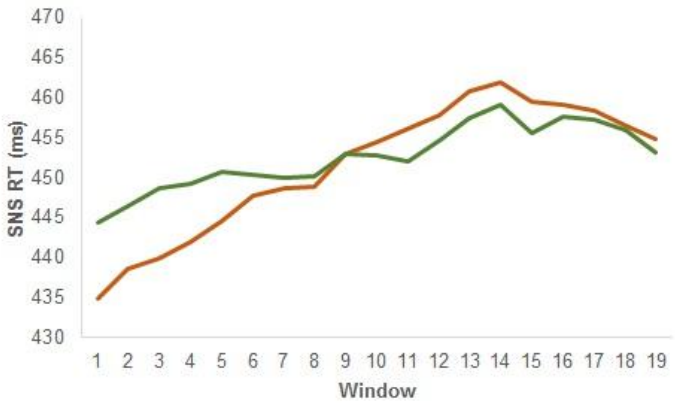


Figure APP10.3.7. The change in reaction time to no-signal trials in the SST (SNS) across windows in the active (orange) and sham (green) conditions.

APP10.3.6.5.2.5. Double no-signal RT: Neither window or cTBS was found to influence the latency of the reaction time to no-signal trials in the double context (Figure APP10.3.8).

Step 1: Determine the random structure and covariance structure

Model	Test	Random	Covariance	LL	df	X^2	*p*
1	Initial REML	1		2771.63	6		
2	Random window 1 vs. 2	1 + window		2820.47	8	$X^2_{(1.5)}$=97.69	<.001
3	Random window 2 vs. 3	1 + window	AR	3810.2	9	$X^2_{(1)}$=1979.45	<.001

Decision test model 2: add random window; decision test model 3; use autoregressive (AR) structure

Step 2: Determine fixed effects

Model	Test	Fixed	LL	df	X^2	*p*
1	Initial ML	site x window	3833.05	9		
2	Remove interaction 1 vs. 3	site + window	3833.04	8	$X^2_{(1)}$=0.03	.855
3	Remove site 2 vs. 3	Window	3833.01	7	$X^2_{(1)}$=0.06	.804
4	Remove window 2 vs. 4	Site	3831.71	7	$X^2_{(1)}$=2.66	.103

Decision test model 2: remove interaction; decision tests model 3: remove site; decision test model 4: remove window

No further analyses conducted as no fixed effects contributed significantly to the model fit.

Figure APP10.3.8. The change in RT to no-signal trials in the DT (DNS) across windows in the active (orange) and sham (green) conditions.

APP10.3.6.5.3 Exploration of cTBS induced changes in %BOLD in ROIs remote to the site of application

Table APP10.3.7. Paired sample t-tests exploring the effect of cTBS on BOLD activity within ROIs remote to the site of cTBS application under active vs. sham conditions.

	Stop				Double			
ROI	t	df	*p*	BF	t	df	*p*	BF
R pre-SMA	1.83	29	.077	0.85	-1.56	27	.131	0.59
R STR	0.04	28	.965	0.2	-0.82	27	.41	0.27
R GPe	0.04	28	.965	0.2	-0.27	29	.787	0.20
R GPi	-0.4	29	.693	0.21	-0.41	29	.687	0.21
R STN	-0.53	29	.598	0.22	-0.6	29	.552	0.23
R SN	-1.05	29	.303	0.32	-0.01	28	.995	0.2
R THAL	-0.58	29	.568	0.23	-1.29	29	.208	0.41
L pre-SMA	-0.01	28	.99	0.2	-0.48	28	.632	0.22
L STR	-0.38	29	.710	0.21	-0.39	28	.699	0.21
L GPe	0.57	27	.572	0.23	-0.87	29	.393	0.28
L GPi	-1.33	29	.193	0.43	-0.41	28	.684	0.2
L STN	-1.18	29	.249	0.37	-0.87	28	.392	0.2
L SN^{++}	-1.31	28	.201	0.43	-0.09	28	.377	0.29
L THAL	-1.31	27	.201	0.43	-1.66	29	.109	0.66

Note. Analysis were conducted on %BOLD in each region of interest (**ROI**) acquired from the signal>no-signal contrasts in the SST and DT. **t**=t-value; **df=** degrees of freedom; ***p***=*p*-value; **BF**=Bayes Factor; **R**=right; **L**=left; **pre-SMA**=pre-Supplementary Motor Area; **STR**= striatum; **GPe**= globus pallidus externa; **GPi**= globus pallidus interna; **STN**= subthalamic nucleus; **SN**= substantia nigra; **THAL**= thalamus. Note that for any BFs calculated for GABA-related data the prior scale factor was reduced by √2 (see section 4.4.2). All degrees of freedom=29. α-level for Holm-Bonferonni comparison not shown as all *p*>.05. $^{++}$= non-parametric analysis required for stop analysis only.

Wilcoxon sign rank sum testst for LSN to explore whether there is a change in %BOLD between active and sham sessions.

Without outlier remova: Z=1.41, *p*=.159, N=30. Without outliers: Z=1.16, *p*=.247, N=29.

10.4. Appendices for Chapter 5.

APP10.4.1. Replication of cortical findings

Paired sample t-tests were run to establish if there were %BOLD differences in the rIFG and pre-SMA between the SST and DT condition.

Subsequent to outlier exclusion. rIFG: $t_{(28)}$=1.22, *p*=.232, BF=0.39; *pars opercularis*: $t_{(27)}$=0.91, *p*=.373, BF=0.29; *pars triangularis*: $t_{(28)}$=0.54, *p*=.597, BF=0.23; pre-SMA : $t_{(28)}$=2.23, *p*=.03, BF=1.65.

Non-parametric tests required. rIFG : Z=-1.20, *p*=.229 ; *pars opercularis:* Z=-1.45, *p*=.147.

APP10.4.2. Replication of pathways analyses

Table APP10.4.1. Contrasts and categorisation of contrasts computed for the replication of the pathways analyses conducted in Study 2.

Unclear									
Response execution			**Proactive**				**Reactive**	
DA	DS	DNS	SA	FS	SNS	SSI	SS	SSC
DA>SA	DS>SA	DNS>SA	SA>DA	FS>DA	SNS>DA	SSI>DA	SS>DA	SSC>SA
DA>FA	DS>FA	DNS>FA	SA>FA	FS>FD	SNS>FA	SSI>FA	SS>FA	SSC>DA
DA>FS	DS>FS	DNS>FS	SA>FD	FS>DS	SNS>FD	SSI>FD	SS>FS	SSC>FA
DA>FD	DS>FD	DNS>FD	SA>DS	FS>DNS	SNS>DS	SSI>DS	SS>FD	SSC>FS
DA>SS	DS>SS	DNS>SS	SA>DNS	FS>SSI	SNS>DNS	SSI>DNS	SS>SNS	SSC>FD
DA>SNS	DS>SNS	DNS>SNS					SS>DS	SSC>SNS
DA>SSC	DS>DNS	DNS>SSC					SS>DNS	SSC>DS
DA>SSI	DS>SSC	DNS>SSI						SSC>DNS
	DS>SSI							SSC>SSI

FA	FD	SA>FS	SNS>FS	SSI>SA
FA>SA	FD>SA	SA>SSC	SNS>SS	SSI>FS
FA>DA	FD>DA	SA>SSI	SNS>SSC	SSI>SNS
FA>SS	FD>FS	FS>SA	SNS>SSI	SSI>SSC
FA>SNS	FD>SS	FS>SS	DNS>DS	
FA>DS	FD>SNS	FS>SNS		
FA>DNS	FD>DS	FS>SSC		
FA>SSC	FD>DNS			
FA>SSI	FD>SSC			
	FD>SSI			

Note. **FA**=all fixations across contexts, **FD**= fixations in the DT, **FS**=fixations in the SST, **DA**=all DT trials, **SA**= all SST trials, **DNS**=double no-signal trials, **DS**=double-signal trials, **SNS**= stop no-signal trials, **SS**= stop-signal trials, **SSC**=correct stop signal trials, **SSI**= incorrect stop-signal trials. Contrasts are colour-coded as to whether relate to the DT (green), SST (red) or no particular context (grey).

APP10.4.2.2. Re-analysis of pathways data with the ignore condition excluded.

Here, data acquired in Study 1 were re-analysed with the exclusion of all contrasts that related to the ignore context. This was to establish what influence the IT had on the subsequent patterns of activity under response execution and response inhibition conditions.

Models were fit to the pathways they were expected to converge to (Table APP10.4.2.) and opposing models (Table APP10.4.3). See section 3.2.2.1 for original analyses.

Table APP10.4.2. Data fit to models from Study 1 but contrasts related to ignore context removed.

Pathway		t	df	*p*	BF	JZS
Direct		2.56	29	.008	6	3.13
Indirect	Proactive	1.53	29	.069	0.71	0.55
	Reactive	3.17	29	.002	27.91	10.73
	All	2.91	29	.003	14.45	6.18
Hyperdirect	Proactive	1.26	29	.109	0.67	0.4
	Reactive	3.07	29	.002	28.1	8.66
	All	2.59	29	.008	8.52	3.22

Note. **t**=t-value; **df**= degrees of freedom; **BF**=Bayes Factor; **JZS**=model fits using JZS prior; **Proactive**= contrasts categorised as proactive inhibition; **Reactive**= contrasts categorised as reactive inhibition; **All**= all contrasts categorised as inhibition regardless of whether proactive or reactive.

Table APP10.4.3. Data fit to incorrect models from Study 1 but contrasts related to ignore context removed.

Pathway	t	df	*p*	BF	JZS
Direct	-0.03	29	.511	0.2	0.11
Indirect	-0.95	29	.826	0.3	0.05
Hyperdirect	-0.56	29	.71	0.23	0.11

Note. Here, all contrasts categorised as response inhibition were fit to the direct pathway model, whilst all contrasts categorised as response execution were fit to the indirect and hyperdirect pathway models. **t**=t-value; **df**= degrees of freedom; **BF**=Bayes Factor; **JZS**=BFs using JZS prior.

To assess the lateralised distribution of activity across BG ROIs under conditions of response execution and response inhibition a 3-way ANOVA was computed with (execution vs. inhibition) and site (8 levels, bilateral representation of each subcortical and cortical ROI) and hemisphere (left vs. right) as factors as applied to the raw %BOLD.Contrary to original analyses there was no main effect of condition ($F_{(1,29)}$=3.52, p=.071, but all other main effect and interaction effects remained, including the important interaction between hemisphere and condition ($F_{(1,29)}$=41.32,

$p<.001$)[132] and was followed by simple effects analyses (Table APP10.4.4) and moderator/mediator analyses (Table APP10.4.5 and Table APP10.4.6). See sections 3.2.2.2 and 3.2.2.3 for original analyses.

[132] Consistent with the original analysis of Study 1 data, main effects of site ($F_{(7,203)}=6.08$, $p<.001$) and hemisphere ($F_{(1.29)}=19.27$, $p<.001$) were observed, as were the significant interactions between condition and site ($F_{(7,203)}=12.59$, $p<.001$) and site and hemisphere ($F_{(7,203)}=30.13$, $p<.001$).

Table APP10.4.4. Simple effect analysis of %BOLD in each ROI under conditions of response execution and response inhibition after ignore-related contrasts were excluded.

		Execution vs. Inhibition			Execution			Inhibition		
Hem	ROI	t	*p*	BF	t	*p*	BF	t	*p*	BF
Left	pre-SMA	0.43	.668	0.21	1.17	**.253**	0.36	0.95	.35	0.29
	IFG	**-3.57**	.001	**27.10**	**-5.01**	**<.001**	**917.96**	1.06	.296	0.32
	STR	**2.91**	.007	**6.22**	**4.82**	**<.001**	**565.33**	0.90	.375	0.28
	GPe	**2.58**	.015	**3.18**	**4.07**	**<.001**	**89.03**	0.58	.567	0.23
	GPi	0.4	.693	0.21	1.13	**.269**	0.35	0.67	.511	0.24
	SN	0.22	.828	0.2	1.45	**.457**	0.50	1.22	.234	0.38
	STN	-0.45	.655	0.21	10.48	**.638**	0.22	1.5	.145	0.53
	THAL	**2.69**	.012	**3.91**	**3.78**	**<.001**	**44.46**	-0.63	.537	0.23
Right	pre-SMA	**-4.73**	<.001	**456.42**	-0.8	**.432**	0.26	**7.65**	<.001	**1.59E+05**
	IFG	**-8.48**	<.001	**4.95E+06**	**-4.85**	**<.001**	**619.65**	**8.59**	<.001	**6.37E+06**
	STR	-0.6	.555	0.23	**2.91**	**.007**	**6.16**	**4.01**	<.001	**76**
	GPe	0.64	.528	0.24	**3.07**	**.005**	**8.75**	**2.52**	.018	2.8
	GPi	0.43	.669	0.21	0.66	**.512**	0.24	-0.67	.945	0.2
	SN	**-2.52**	.018	2.8	-1.27	.215	0.40	**3.57**	.001	**26.57**
	STN	**-2.21**	.035	1.59	-0.7	.495	0.24	**3.61**	.001	**29.75**
	THAL	-1.62	.117	0.62	-0.31	.756	0.20	**3.54**	.001	**25.123**

Note**.** Analyses were conducted separately for each region of interest (**ROI**) when responses were to be executed, or inhibited, or compared. **Hem**=hemisphere; **ROI**= region of interest; **t**=t-value, significant t-values are reported in bold; ***p***=*p*-value; **BF**=Bayes Factors, BFs>3 are reported in bold; **STR**=striatum; **GPe**=globus pallidus extern; **GPi**=globus pallidus interna; **STN**=subthalamic nucleus; **SN**=substantia nigra; **THAL**=thalamus; **IFG**=inferior frontal gyrus; **pre-SMA**=pre-supplementary motor area. All degrees of freedom=29.

Table APP10.4.5. The moderating and mediating effects of the addition of covariates under conditions of response execution.

			Left				Right		
Hem	ROI	Original	IFG	STR	GPe	THAL	IFG	STR	GPe
Left	IFG	<.001		<.001	<.001	<.001	.043	<.001	<.001
		917.96		**5.71E+03**	**893.28**	**1.43^{E+03}**	**1.38**	**1.36^{E+03}**	**195.95**
	STR	<.001	<.001		.034	.023	<.001	<.001	.003
		565.33	**3.57^{E+03}**		**1.67**	**2.24**	**714.64**	**94.28**	**13.22**
	GPe	<.001	<.001	.372		.091	<.001	.019	.026
		89.03	**94.21**	**0.29**		**0.76**	**254.82**	**2.72**	**2.07**
	THAL	<.001	<.001	.932	.229		<.001	.045	.032
		44.46	**87.83**	**0.2**	**0.39**		**235.31**	**1.32**	**1.74**
Right	IFG	<.001	.069	<.001	<.001	<.001		<.001	<.001
		619.66	**0.95**	**780.76**	**1.66^{E+03}**	**3.03^{E+03}**		**1.45^{E+04}**	**1.08^{E+03}**
	STR	.007	.004	.049	.706	.871	<.001		.213
		6.16	**10.86**	**1.23**	**0.21**	**0.2**	**165.78**		**0.41**
	GPe	.005	.023	.498	.596	.249	.002	.133	
		8.75	**2.24**	**0.24**	**0.23**	**0.367**	**17.84**	**0.57**	

Note. BFs are shown in bold below the corresponding *p*-value. The original values correspond to those yielded from the simple effects analysis (Table APP10.4.4). The table can be read from left to right, where the regions of interest in each column are the covariate added to the moderator/mediator analyses. **L**=left hemisphere; **R**=right hemisphere; **pre-SMA**=pre-supplementary motor area; **IFG**=inferior frontal gyrus; **STR**=striatum; **GPe**=globus pallidus externa; **THAL**=thalamus; **N/A**= no corresponding BF as criteria of BF>3 not met via simple effects analyses. Values highlighted in blue represent instances of moderation, where the significance of the *p*-value after addition of a covariate is reduced (i.e. *p*-value increased) but the significance remains (i.e. *p*<.05; for Bayesian equivalent, BF<3, but >1/3). Values highlighted in orange represent instances of mediation, where the *p*-value is increased to >.05 after addition of the covariate (i.e. no longer significant; for Bayesian equivalent, BF<1/3).

Table APP10.4.6. The moderating and mediating effects of the addition of covariates under conditions of response inhibition.

			Right						
Hem	ROI	Original	pre-SMA	IFG	STR	GPe	SN	STN	THAL
Right	pre-SMA	<.001		.313	<.001	<.001	<.001	<.001	<.001
		1.59^{E+05}		**0.32**	**788.15**	**N/A**	**1.01^{E+03}**	**1.02^{E+03}**	**1.20^{E+03}**
	IFG	<.001	.004		<.001	<.001	<.001	<.001	<.001
		6.37^{E+06}	**10.4**		**1.25^{E+04}**	**N/A**	**2.81^{E+04}**	**2.76^{E+04}**	**7.37^{E+04}**
	STR	<.001	.148	.486		.008	.033	.076	.07
		76	**0.53**	**0.25**		**N/A**	**1.69**	**0.87**	**0.94**
	GPe	.018	.538	.067	.56		.332	.607	.685
		N/A	**N/A**	**N/A**	**N/A**		**N/A**	**N/A**	**N/A**
	SN	<.001	.488	.829	.12	.019		.266	.093
		26.57	**0.25**	**0.20**	**0.62**	**N/A**		**0.35**	**0.75**
	STN	<.001	.389	.623	.263	.025	.226		.138
		29.75	**0.28**	**0.22**	**0.36**	**N/A**	**0.4**		**0.56**
	THAL	<.001	.392	.175	.304	.032	.099	.173	
		25.13	**0.28**	**0.47**	**0.33**	**N/A**	**0.71**	**0.47**	

Note. BFs are shown in bold below the corresponding *p*-value. The original values correspond to those yielded from the simple effects analysis (Table 10.4.4). The table can be read from left to right, where the regions of interest in each column are the covariate added to the moderator/mediator analyses. **L**=left hemisphere; **R**=right hemisphere; **pre-SMA**=pre-supplementary motor area; **IFG**-inferior frontal gyrus; **STR=**striatum; **GPe**=globus pallidus externa; **SN**=substantia nigra; **STN**=subthalamic nucleus; **THAL**=thalamus. Values highlighted in blue represent instances of moderation, where the significance of the *p*-value after addition of a covariate is reduced (i.e. *p*-value increased) but the significance remains (i.e. *p*<.05; for Bayesian equivalent, BF<3, but >1/3). Values highlighted in orange represent instances of mediation, where the *p*-value is increased to >.05 after addition of the covariate (i.e. no longer significant; for Bayesian equivalent, BF<1/3).

10.5. Appendices for Chapter 6.

APP10.5.1. Results.

Results here include analyses with outliers excluded and non-parametric tests (if applicable). The results with no outliers removed are reported in the main text. Discrepancies between results are discussed in the main text.

APP10.5.1.1. Analysis of cardio-respiratory data.

Repeated measures ANOVA of respiration rate differences in Study 1. Significant difference in respiration rates revealed between contexts ($F_{(2,54)}$=10.02, p<.001, BF=122.85), whereby the respiration rate in the DT was greater than in the IT ($p_{.0167}$<.001, BF=529.66), but other relationships proved inconclusive (DT>SST: p=.056, BF=1.13; SST>IT, $p_{.025}$=.03, BF=1.87).

Paired sample t-tests for respiration rate in Study 2 revealed significantly greater rates associated with the DT relative to the SST ($t_{(28)}$=2.54, p=.017, BF=2.93). No difference between contexts with respect to cardiac rate was found ($t_{(27)}$=0.61,p=.55, BF=0.24).

APP10.5.1.1.1. Correlation analyses between cardiac and respiration rates with behavioural indices of action updating

Table APP10.5.1. Summary of correlations conducted between cardiac rate and behavioural indices of action updating and between respiration rate and behavioural indices of action updating in Studies 1 and 2.

Study	DVs		r	df	*p*	BF
Study 1	Mean SSRT	Stop Cardiac	0.4	27	.032*****	1.76
		Stop Resp	-0.19	26	.341	0.31
	Integ SSRT	Stop Cardiac	0.28	27	.141	0.55
		Stop Resp	-0.39	25	.044*****	1.38
	p(respond|signal)	Stop Cardiac	-0.27	27	.154	0.51
		Stop Resp	-0.12	26	.559	0.24
	DRT2	Double Card	-0.22	23	.284	0.36
		Double Resp	-0.05	26	.794	0.21
	Bottleneck	Double Card	-0.21	26	.279	0.35
		Double Resp	0.16	25	.413	0.27
Study 2	Integ SSRT	Stop Cardiac	0.1	27	.595	0.22
		Stop Resp	0.14	25	.486	0.26
	p(respond|signal)$^{+}$	Stop Cardiac	0.1	27	.610	0.22
		Stop Resp	0.2	27	.292	0.33
	DRT2	Double Card	0.4	27	.031*****	1.76
		Double Resp	0.08	26	.689	0.22
	Bottleneck	Double Card	-0.31	25	.116	0.66
		Double Resp	-0.32	26	.102	0.74

Note. **DVs**=dependent variables; **r=**Pearson's correlation coefficient; ***p***=p-value; **BF**= Bayes Factor; **Mean SSRT**= SSRT as estimated via the mean method; **Integ SSRT**= SSRT as estimated via the integration method; **p(respond|signal)**= the probability of responding to a stop signal trial; **DRT2**=the latency of the double-response process; **Bottleneck**= size of the bottleneck on double-signal trials as quantified in Section 2.3.1. $^{+}$=non-parametric tests required. *****= does not survive Holm-Bonferroni correction for α (**=**.025).

Non-parametric Spearman's rho conducted for relationships between cardio-respiratory measures and *p*(respond|signal).

Cardiac rate and *p*(respond|signal): With outliers; $rs_{(28)}$=0.05, *p*=.787; without outliers: $rs_{(27)}$=0.1, *p*=.605).

Respiration rate and *p*(respond|signal): With outliers: $rs_{(28)}$=0.07, *p*=.696; without outliers: $rs_{(26)}$=0.04, *p*=.836).

APP10.5.1.2. Analysis of Study 3 data

APP10.5.1.2.1. Analysis of behavioural data.

RTs to stop no-signal trials were longer than RTs to unsuccessful stop signal trials ($t_{(28)}$=9.89, p<.001, BF=8.22^{e+7}).

APP10.5.1.2.2. Analysis of self-report data.

Correlations were established between measures of task-related difficulty and frustration for each task. Stop: $r_{(26)}$=0.87, $p_{.0167}$<.001, BF=6.46^{e+6}; Double: $r_{(26)}$=0.84, $p_{.025}$<.001, BF=6.07^{e+5}; Ignore: $r_{(25)}$=0.88, $p_{.05}$<.001, BF=7.92^{e+6}.

Repeated measures ANOVA of task-related frustration across the contexts revealed significant difference ($F_{(2,56)}$=112.82, p<.001. BF=1.37^{e+19}). The SST was more frustrating than the DT (p<.001, BF=1.17^{e+9}) and the IT (p<.001, BF=1.44^{e+10}). The DT was reported to be more frustrating than the IT (p=.013, BF=3.72).

APP10.5.1.2.2.1. Relationships between task-related difficulty, task-related frustration and behavioural indices of action updating.

Table APP10.5.2. Summary of correlations between behavioural indices of action updating and self-report ratings of task-related difficulty and frustration.

DVs		r	df	*p*	BF
SSRT	S Diff	-0.24	27	.207	0.76
	S Frust	-0.15	27	.427	0.26
p(respond|signal)	S Diff	0.26	27	.172	0.47
Proac Slow^{+}	S Frust	-0.19	27	.320	0.31
DRT2	D Frust	-0.25	25	.217	0.43
Bottleneck	D Diff	0.01	26	.980	0.2
	D Frust	-0.02	27	.936	0.2

Note. **DVs**=dependent variables; **r**=Pearson's correlation coefficient; **df**=degrees of freedom; ***p***=*p*-value; **BF**-Bayes Factor; **SSRT**=stop signal reaction time as estimated via the integration method; **p(respond|signal)**=the probability of responding on a stop signal trial; **Proac Slow=**proactive slowing, computed as the difference between the reaction time on no-signal trials in the ignore context subtracted from those in the stop context; **DRT2**= the latency of the non-inhibitory updating process; **Bottleneck**= the size of the bottleneck as quantified via the procedure outlined in Section 2.3.1; **Diff**=task-related difficulty; **Frust**=task-related frustration; $^{+}$=computed based on square-root transformed data. α-level for comparison not shown as all p>.05.

APP10.5.1.2.3. Pupillometry analysis.

Pupil diameter was found to be increased on signal relative to no-signal trials in the SST ($t_{(27)}$=0.15, *p*=.879, BF=0.2) and IT ($t_{(27)}$=0.27, *p*=.791, BF= 0.2), but not reliably so.

Pupil diameter on double signal trials was significantly greater than on double no-signal trials ($t_{(28)}$=4.23, *p*<.001. BF=7.28).

Pupil diameter was greater for double no-signal trials relative to stop signal trials, but this was not reliable ($t_{(27)}$=1.74, *p*=.093, BF=0.76).

Non-parametric Wilcoxon signed rank test for the comparison of pupil diameter on double signal vs. double no-signal trials. With outliers: Z=-1.57, N=30, *p*=.116; without outliers: Z=-1.753, N=28, *p*=.080.

APP10.5.1.2.3.1. Correlational analyses between pupil diameter and behavioural indices of action updating.

Table APP10.5.3. Summary of correlations between behavioural indices of action updating and pupil diameter across the SST and DT.

DVs		r	df	*p*	BF
SSRT	SST All	0.02	26	.940	0.2
	SS	0.03	26	.873	0.2
	SNS	0.01	26	.974	0.2
p(respond|signal)	SST All	-0.1	26	.597	0.23
	SS	-0.11	26	.565	0.23
	SNS	-0.1	26	.614	0.23
Proac Slow^{+}	SST All	0.13	25	.525	0.25
	SS	0.14	25	.497	0.26
	SNS	0.02	26	.913	0.2
DRT2	DT All	0.18	27	.351	0.3
	DS	0.18	27	.347	0.3
	DNS	0.18	27	.354	0.3
Bottleneck	DT All	0.33	27	.084	0.84
	DS	0.33	27	.084	0.84
	DNS	0.33	27	.084	0.84

Note. **DVs**=dependent variables; **r**=Pearson's correlation coefficient; ***p***=*p*-value; **BF**-Bayes Factor; **SSRT**=stop signal reaction time as estimated via the integration method; **p(respond|signal)**=the probability of responding on a stop signal trial; **Proac Slow=**proactive slowing, computed as the difference between the reaction time on no-signal trials in the ignore context subtracted from those in the stop context; **DRT2**= the latency of the non-inhibitory updating process; **Bottleneck**= the size of the bottleneck as quantified via the procedure outlined in Section 2.3.1; **Diff**=task-related difficulty; **Frust**=task-related frustration; $^{+}$=computed based on square-root transformed data. α-level for comparison not shown as all *p*>.05.

APP10.5.1.2.3.2. Correlational analyses between pupil diameter and self report measures of task-related frustration and difficulty.

Table APP10.5.4. Summary of correlations between self-report measures of task-related difficulty and frustration with pupil diameter across the SST, DT and IT.

DVs		r	df	*p*	α	BF
SST Diff	S All	-0.41	26	.029		1.85
	SNS	-0.41	26	.029		1.85
	SS	-0.42	26	.028	.0167	2.08
SST Frust	S All	-0.4	26	.038		1.64
	SNS	-0.39	26	.039		1.47
	SS	-0.4	26	.036	.0167	1.64
DT Diff	D All	0.05	28	.813		0.2
	DNS	0.04	28	.816		0.2
	DS	0.05	28	.808		0.2
DT Frust	D All	-0.41	26	.031	.0167	1.85
	DNS	-0.41	26	.031		1.85
	DS	-0.41	26	.032		1.85
IT Diff^{+}	I All	0.07	27	.703		0.21
	INS	0.07	27	.704		0.21
	IS	0.08	27	.700		0.21
IT Frust^{+}	I All	0.15	27	.458		0.26
	INS	0.15	26	.460		0.26
	IS	0.15	26	.458		0.26

Note. **DVs**=dependent variables; **r**=Pearson's correlation coefficient; ***p***=*p*-value; **BF**-Bayes Factor; **Diff**=task-related difficulty; **Frust**=task-related frustration; **All**=mean pupil diameter across all trials within the corresponding context; **NS**= mean pupil diameter across no-signal trials within the corresponding context; **SS/DS/IS**= mean pupil diameter across signal trials in the corresponding context; $^{+}$=computed based on square-root transformed data. α calculated as: $\alpha(k)=0.05/(n-k+1)$, where n is the number of ROIs (in this case 3), and k is the rank ordering of p-values from 1 to n.

10.6. Appendices for Chapter 7.

APP.10.6.1. Results

RTs to signal (i.e. unsuccessful stops) and no-signal trials in the SST for Study 3 ($t_{28)}$=10.05,*p*<.001, BF=1.15^{e+8}).

APP10.6.2. Re-analysis of Study 1-3 data with violations of independent race model excluded

Where violations of the independent race model were identified in Studies 1-3, corresponding analyses were re-run with data corresponding to violations excluded. Note, this pertained only to analyses for which SSRT were included. Data presented below are divided according to Chapter they refer to.

APP10.6.2.1. Chapter 2: 3 participants excluded.

Here, re-analysis was carried out for the following:

18. Correlation between %BOLD and SSRT as estimated using the mean method (Table APP10.6.1). This made no difference to the interpretation of the data.

19. Correlation between %BOLD and SSRT as estimated using the integration method (Table APP10.6.2). This made no difference to the interpretation of the data.

20. Independent sample t-tests for %BOLD and short vs. long SSRTs (as estimated via the mean method and subsequent to a median split; Table APP10.6.3 and APP10.6.4). Re-analysis was found to reduce BFs for some ROIs to <3. Evidence is still in favour of an effect, but is inconclusive.

21. Independent sample t-tests for %BOLD and short vs. long SSRTs (as estimated via the integration method and subsequent to a median split; Table APP10.6.5 and APP10.6.6). Re-analysis was found to increase the left SN from BF>1/3 to a BF of 2.288. This made no difference to the interpretation of the data.

22. Correlation between SSRT as estimated using the mean method and cardiac rate (reported in Chapter 6). Original result: $r_{(28)}$=0.27, *p*=.14, BF=0.52. Re-analysis: $r_{(25)}$=0.26, *p*=.19, BF=0.46. This made no difference to the interpretation of the data.

23. Correlation between SSRT as estimated via the integration method and cardiac rate (reported in Chapter 6). Original result: $r_{(28)}$=0.17, *p*=.371, BF=0.28. Re-analysis: $r_{(25)}$=0.17, *p*=.39, BF=0.29. This made no difference to the interpretation of the data.

24. Correlation between SSRT as estimated via the mean method and respiration rate (reported in Chapter 6). Original result: $r_{(28)}$=-0.12, *p*=.515, BF=0.23. Re-analysis: $r_{(25)}$=-0.14, *p*=.484, BF=0.26. This made no difference to the interpretation of the data.

25. Correlation between SSRT as estimated via the integration method and respiration rate (reported in Chapter 6). Original result: $r_{(28)}$=-0.16, *p*=.408, BF=0.27. Re-analysis: $r_{(25)}$=-0.17, *p*=.189, BF=0.29. This made no difference to the interpretation of the data.

Table APP10.6.1. Correlations between % signal change associated with stop signal>stop no-signal and stop signal reaction time as estimated via the mean method.

	Original results				Re-analysis			
ROI	r	*p*	α	BF	r	*p*	α	BF
R IFG	0.2	.294		0.33	0.2	.311		0.33
R preSMA	0.18	.331		0.3	0.16	.427		0.27
R STR	0.37	.044		1.32	0.38	.049		1.24
R GPe	0.36	.048		1.89	0.37	.059		1.12
R GPi	0.13	.510		0.24	0.12	.555		0.24
R STN	0.29	.126		0.61	0.06	.778		0.21
R SN^{++}	0.18	.331		0.3	0.22	.272		0.36
R THAL^{+}	-0.27	.156		0.52	-0.27	.176		0.49
L IFG	0.01	.968		0.19	0.04	.828		0.21
L preSMA	0.19	.307		0.31	0.19	.351		0.31
L STR	0.26	.169		0.48	0.28	.158		0.52
L GPe	0.36	.053		1.19	0.38	.050		1.24
L GPi	0.33	.077		0.87	0.37	.061		1.12
L STN^{+}	-0.18	.352		0.3	-0.23	.268		0.38
L SN^{++}	0.43	.017	.0028	2.8	0.46	.015	.0028	**3.2**
L THAL	0.19	.328		0.31	0.22	.278		0.36
R pars op	0.22	.236		0.37	0.25	.215		0.43
R pars tri	0.16	.412		0.27	0.13	.507		0.25

Note. **Original results**= those results from Study 2; **Re-analysis**= re-analysis of data with participants who violate independence assumptions excluded; **ROI**= region of interest; **r=** coefficient value; ***p***=p-value; **α**= alpha level for comparison after Holm-Bonferonni correction; **BF**=Bayes Factors; **R**=right; **L**=left; **IFG**=inferior frontal gyrus; **preSMA**=pre-supplementary motor area**; STR**=striatum; **GPe**=globus pallidus externa; **GPi**=globus pallidus interna; **STN**=subthalamic nucleus; **SN**=substantia nigra; **THAL**=thalamus; **pars op**= pars opercularis; **pars tri**= pars triangularis; $^{+}$= analysis conducted on transformed data, $^{++}$=non-parametric required. Degrees of freedom for original results=28; degrees of freedom for re-analysed data=25. α-level for comparison shown in accord with Holm-Bonferroni method (Aickin & Gensler, 1996).

Spearman's correlations were computed for %BOLD in the right and left SN with SSRT as computed using the integration method.

RSN: Original result: $rs_{(28)}$=0.05, p=.784. Re-analysis result: $rs_{(25)}$=0.11, p=.575.

LSN: Original result: $rs_{(28)}$=0.31, p=.840. Re-analysis result: $rs_{(25)}$=0.42, $p_{.0028}$=.029.

Table APP10.6.2. Correlations between % signal change associated with stop signal>stop no-signal and stop signal reaction time as estimated using the integration method.

	Original results			Re-analysis		
ROI	r	*p*	BF	r	*p*	BF
R IFG	0.23	.221	0.39	0.23	.243	0.38
R preSMA	0.18	.349	0.3	0.14	.483	0.26
R STR	0.34	.069	0.96	0.35	.070	0.92
R GPe	0.32	.086	0.79	0.32	.107	0.71
R GPi	0.09	.654	0.22	0.08	.688	0.22
R STN	-0.05	.814	0.2	-0.03	.878	0.21
R SN	0.11	.566	0.23	0.15	.449	0.27
R THAL	-0.25	.189	0.45	-0.25	.213	0.43
L IFG	0.02	.924	0.2	0.04	.858	0.21
L preSMA	0.23	.216	0.39	0.21	.298	0.34
L STR	0.21	.266	0.35	0.23	.242	0.38
L GPe	0.29	.126	0.61	0.31	.122	0.66
L GPi	0.26	.173	0.48	0.3	.136	0.61
L STN	-0.01	.947	0.19	-0.07	.735	0.22
L SN	0.34	.062	0.96	0.38	.054	1.24
L THAL	0.19	.326	0.31	0.19	.351	0.31
R pars op	0.23	.223	0.39	0.25	.201	0.43
R pars tri	0.21	.274	0.35	0.18	.382	0.3

Note. **Original results**= those results from Study 2; **Re-analysis**= re-analysis of data with participants who violate independence assumptions excluded; **ROI**= region of interest; **r=** coefficient value; ***p***=p-value; **BF**=Bayes Factors; **R**=right; **L**=left; **IFG**=inferior frontal gyrus; **preSMA**=pre-supplementary motor area**; STR**=striatum, **GPe**=globus pallidus externa; **GPi**=globus pallidus interna; **STN**=subthalamic nucleus; **SN**=substantia nigra; **THAL**=thalamus; **pars op**= pars opercularis; **pars tri**= pars triangularis; $^{+}$= analysis conducted on transformed data; $^{++}$=non-parametric required. Degrees of freedom for original results=28; degrees of freedom for re-analysed data=25. α-level for comparison not shown as all *p*>.05.

Spearman's correlations were computed for %BOLD in the right and left SN with SSRT as computed via the integration method.

RSN: Original result: $rs_{(28)}$=0.04, *p*=.837. Re-analysis result: $rs_{(25)}$=0.1, *p*=.628.

LSN: Original result: $rs_{(28)}$=0.29, *p*=.118. Re-analysis result: $rs_{(25)}$=0.36, *p*=.063.

Table APP10.6.3. Summary of independent t-results for % signal change within regions of interest for short vs. long stop signal reaction times as estimated via the mean method.

	Original results				Re-analysis			
ROI	t	*p*	α	BF	t	*p*	α	BF
R IFG	-1.34	.191		0.69	-1.24	0.23		0.65
R preSMA	-0.7	.493		0.42	0.29	0.366		0.51
R STR	-2.55	.017		**3.47**	0.42	0.04		1.91
R GPe	-2.79	.01	.0028	**5.23**	-2.4	0.026	.0028	2.62
R GPi	-1.21	.239		0.61	-0.99	0.333		0.53
R STN	-0.46	.647		0.38	-0.43	0.671		0.4
R SN	-0.43	.675		0.38	-0.68	0.501		0.44
R THAL	-2.15	.041		1.84	-1.77	0.09		1.13
L IFG	-0.67	.51		0.42	-0.97	0.342		0.53
L preSMA	-0.58	.567		0.4	0.94	0.503		0.44
L STR	-2.03	.053		1.56	-1.78	0.089		1.14
L GPe	-2.56	.017		**3.49**	0.23	0.043		1.83
L GPi	-1.79	.086		1.13	-1.57	0.13		0.9
L STN	0.94	.358		0.49	1.3	0.203		0.69
L SN	-1.91	.067		1.33	-2.29	0.032		2.24
L THAL	-1.69	.102		1.01	-1.41	0.173		0.76
R pars op	-1.4	.173		0.73	-1.3	0.207		0.68
R pars tri	-1.23	.229		0.62	-1.11	0.28		0.68

Note. **Original results**= those results from Study 2; **Re-analysis**= re-analysis of data with participants who violate independence assumptions excluded. Note than in original analyses 2 participants were identical to the median SSRT when estimated via the mean method. To ensure an equal number of participants in the short and long SSRT groups, these data points were excluded. Degrees of freedom for these analyses=27. In the re-analysed data SSRTs for 2 participants were identical to the median SSRT when estimated via the mean method. To ensure an equal number of participants in the short and long SSRT groups, these data points were excluded as well as an additional participant, whose data corresponded to the new median value. Degrees of freedom for these analyses=22. **ROI**= region of interest; **t=** t-value; ***p***=p-value; **α**= alpha level; **BF**=Bayes Factors, BFs>3 are reported in bold; **R**=right; **L**=left; **IFG**=inferior frontal gyrus; **preSMA**=pre-supplementary motor area**; STR**=striatum; **GPe**=globus pallidus externa; **GPi**=globus pallidus interna; **STN**=subthalamic nucleus; **SN**=substantia nigra; **THAL**=thalamus; **pars op**= pars opercularis; **pars tri**= pars triangularis; $^{+}$=analyses conducted on transformed data; $^{++}$=non-parametric analysis required. α-level for comparison shown in accord with Holm-Bonferroni method (Aickin & Gensler, 1996).

Table APP10.6.4. Summary of non-parametric Mann-Whitney U tests for % signal change within regions of interest for short vs. long stop signal reaction times as estimated via the mean method.

	Original		Re-analysis	
	U	*p*	U	*p*
R GPe	154	.009	86	.443
R STN	88	.667	66	.755
R SN	99	<.999	80	.671
L IFG	114	.482	89	.347
L SN	134	.104	113	.017

Note. Results are for those data sets that demonstrate violations of the normality assumption. **Original results**= those results from Study 2; **Re-analysis**= re-analysis of data with participants who violate independence assumptions excluded. Note for original analyses N=28, for re-analysed data N=24. **ROI**= region of interest; **U=** Mann-Whitney U-value; ***p***=p-value; **α**= alpha level for comparison after Holm-Bonferonni correction; **R**=right; **L**=left; **IFG**=inferior frontal gyrus; **preSMA**=pre-supplementary motor area**; GPe**=globus pallidus externa; **STN**=subthalamic nucleus; **SN**=substantia nigra. α-level for not shown as Holm-Bonferroni procedure would be discontinued when *p*-values for parametric tests accounted for (Table APP10.6.3).

Table APP10.6.5. Summary of independent t-results for % signal change within regions of interest for short vs. long stop signal reaction times as estimated using the integration method.

	Original results				Re-analysis			
ROI	t	*p*	α	BF	T	*p*	α	BF
R IFG	-1.36	.186		0.69	-1.55	.134		0.87
R preSMA	-1.07	.294		0.53	-0.73	.470		0.44
R STR^{++}	-2.47	.020		**3.08**	-2.76	.011		**4.83**
R GPe^{++}	-2.78	.010	.0028	**5.2**	-2.74	.011		**4.69**
R GPi	-0.7	.489		0.42	-0.84	.407		0.47
R STN^{++}	-0.3	.765		0.36	-0.59	.563		0.41
R SN^{+}	0.63	.535		0.4	1.08	.289		0.56
R THAL	-1.68	.104		0.98	-1.77	.090		1.11
L IFG^{++}	-0.49	.625		0.38	-0.59	.558		0.41
L preSMA	-0.69	.497		0.41	-0.41	.685		0.39
L STR^{++}	-2.05	.049		1.64	-2.3	.031		2.29
L GPe	-2.72	.011		**4.66**	-2.9	.008	.0028	**7.09**
L GPi	-1.47	.152		0.77	-1.81	.083		1.17
L STN^{++}	-0.3	.765		0.4	-1.05	.306		2.49
L SN^{++}	-2.33	.027		2.45	-2.35	.027		0.54
L THAL	-1.56	.129		0.85	-1.54	.137		0.85
R pars op	-1.38	.177		0.71	-1.56	.132		0.87
R pars tri	-1.18	.249		0.58	-1.32	.201		0.68

Note. **Original results**= those results from Study 2; **Re-analysis**= re-analysis of data with participants who violate independence assumptions excluded. Note that for re-analysis 1 participant SSRT was identical to the median SSRT. To ensure an equal number of participants in the short and long SSRT groups, this data point was excluded. Degrees of freedom for these analyses=24. Degrees of freedom for original analyses=28. **ROI**= region of interest; **t=** t-value; ***p***=p-value; **α**= alpha level for comparison after Holm-Bonferonni correction; **BF**=Bayes Factors; **R**=right; **L**=left; **IFG**=inferior frontal gyrus; **preSMA**=pre-supplementary motor area**; STR**=striatum, **GPe**=globus pallidus externa; **GPi**=globus pallidus interna; **STN**=subthalamic nucleus; **SN**=substantia nigra; **THAL**=thalamus; **pars op**= pars opercularis; **pars tri**= pars triangularis; $^{+}$=analyses conducted on transformed data; $^{++}$=non-parametric analysis required. BFs>3 are presented in bold. α-level for comparison shown in accord with Holm-Bonferroni method (Aickin & Gensler, 1996).

Table APP10.6.6. Summary of non-parametric Mann-Whitney U tests for % signal change within regions of interest for short vs. long stop signal reaction times as estimated via the integration method.

	Original		Re-analysis	
	U	*P*	U	*p*
R STR	161	.045	129	.022
R GPe	172	.013	133	.012
R STN	94	.461	80	.840
L IFG	119	.806	91	.762
L STR	158	.061	128	.026
L STN	131	.461	110	.191
L SN	166	.026	130	.019

Note. Results are for those data sets that demonstrate violations of the normality assumption. **Original results**= those results from Study 2; **Re-analysis**= re-analysis of data with participants who violate independence assumptions excluded. Note for original analyses N=28, for re-analysed data N=27. To ensure an equal number of participants in the short and long SSRT groups, these data points were excluded as well as an additional participant, whose data corresponded to the new median value. Degrees of freedom for these analyses=22. **ROI**= region of interest; **U=** Mann-Whitney U-value; ***p***=p-value; **α**= alpha level for comparison after Holm-Bonferonni correction; **R**=right; **L**=left; **IFG**=inferior frontal gyrus; **preSMA**=pre-supplementary motor area**;** **GPe**=globus pallidus externa; **STN**=subthalamic nucleus; **SN**=substantia nigra. α-level for not shown as Holm-Bonferroni procedure would be discontinued when *p*-values for parametric tests accounted for (Table APP10.6.5).

APP10.6.2.2. Chapter 4: 4 participants excluded

Here, the following re-analysis was carried out (no differences to interpretation of data were made):

26. The effect of cTBS to the rIFG on SSRT. Original result: $t_{(29)}$=1.1, *p*=.283, BF=0.34. Re-analysis result: $t_{(25)}$=1.07, *p*=.295, BF=0.35.

27. Bayesian meta-analysis of SSRT. Original BF=2.36. Re-analysis BF=2.67.

28. Correlation between GABA and SSRT at baseline. Original result: $r_{(28)}$=-0.37, *p*=.042 (did not survive correction for multiple comparisons), BF=1.32. Re-analysis: $r_{(24)}$=-0.38, *p*=.059, BF=1.17.

29. Correlation between SSRT and rIFG BOLD (as acquired from the contrast stop signal>stop no-signal). Original result: $r_{(28)}$=0.15, *p*=.418, BF=0.26. Re-analysis: $r_{(24)}$=0.17, *p*=.409, BF=0.27.

30. Correlation between cTBS-induced changes in GABA and cTBS-induced changes in SSRT. Original result: $r_{(28)}$=-0.15, *p*=.440, BF=0.26. Re-analysis: $r_{(24)}$=-0.09, *p*=.647, BF=0.23.

31. Correlation between cTBS-induced changes in rIFG BOLD (as acquired from the stop signal>stop no-signal contrast) and cTBS-induced changes in SSRT. Original result: $r_{(28)}$=-0.15, *p*=.429, BF=0.26. Re-analysis: $r_{(24)}$=-0.21, *p*=.311, BF=0.34.

32. Repeated measures ANOVA to assess the influence of cTBS on SSRT over time. Original result: No main effect of cTBS ($F_{(1,28)}$=0.36, *p*=.553, BF=0.18). Main effect of run number (time; $F_{(2.352,65.853)}$=37.18, *p*<.001, Greenhouse-Geisser corrected, BF=21.95). No interaction effect between cTBS and time $F_{(2.036,57.021)}$=0.89, *p*=.419, Greenhouse-Geisser corrected, BF=0.09). SSRT found to gradually increase across run number (all *p*<.001, all BF>21.95, with the exception of run 3>run4: *p*=.467, BF=0.25). Re-analysis: No main effect of cTBS ($F_{(1,24)}$=0.29, *p*=.593, BF=0.18). Main effect of time ($F_{(2.12,51.8)}$=30.91, *p*<.001, Greenhouse-Geisser corrected, BF=3.45^{e+13}). No interaction effect between cTBS and run number ($F_{(1.955, 47.921)}$=0.21, *p*=.781, Greenhouse-Geisser corrected, BF=0.07). SSRT found to gradually increase across run number (all *p*<.001, all BF>47.77, with the exception of run 3>run4: *p*=.81, BF=0.22).

APP10.6.2.2.1. Linear mixed effects, . SSRT:

Influence of cTBS over time, analysed using linear mixed effects. Original outcomes are outlined in Chapter 4. Re-analysis below (note re-analysis made no difference to interpretation of results).

In all tables LL refers to log-likelihood, df=degrees of freedom.

For these analyses, only window was found to significantly contribute to the model fit. SSRT was found to increase steadily across windows in both the active and sham sessions (Figure APP10.6.1).

Step 1: Determine the random structure and covariance of structure

Model	Test	Random	Covariance	LL	df	X^2	*p*
1	Initial REML	1		2049.47	6		
2	Random window 1 vs. 2	1 + window		2100.86	8	$X^2_{(1.5)}$=102.79	<.001
3	Random window 2 vs. 3	1 + window	AR	2707.17	9	$X^2_{(1)}$=1212.6	<.001

Decision test model 2: add random window; decision test model 3: use autoregressive (AR) structure

Step 2: Determine fixed effects

Model	Test	Fixed	LL	df	X^2	*p*
1	Initial ML	site x window	2729.48	9		
2	Remove interaction 1 vs. 3	site + window	2729.37	8	$X^2_{(1)}$=0.22	0.642
3	Remove site 2 vs. 3	window	2729.37	7	$X^2_{(1)}$=0.01	0.933
4	Remove window 2 vs. 4	site	2702.09	7	$X^2_{(1)}$=54.56	<.001

Decision test model 2: remove interaction; decision test model 3: remove site; decision test model 4: keep window

Step 3: Test final model

Effects	F			*p*
Window	F(1,1072)=337.77			<.001
Contrasts	B	SE(B)	T	*p*
Intercept	225.28	7.24	31.13	<.001
Window	2.59	0.14	18.35	<.001

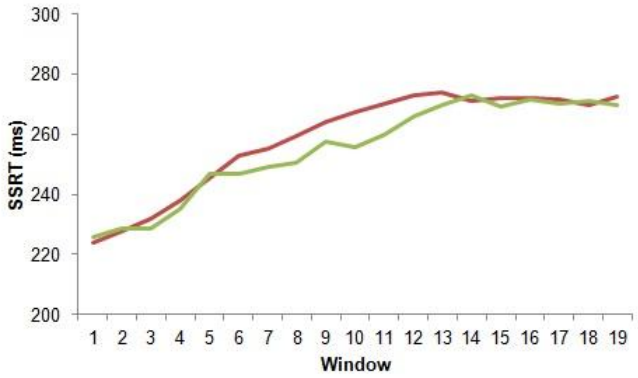


Figure APP10.6.1. The change in stop signal reaction time (SSRT) across windows in the active (orange) and sham (green) conditions.

33. Correlation between SSRT as estimated via the integration method and cardiac rate (reported in Chapter 7). Original result: $r_{(28)}$=-0.02, *p*=.92, BF=0.14. Re-analysis: $r_{(24)}$=0.004, *p*=.983, BF=0.15. No difference to interpretation of data made.

34. Correlation between SSRT as estimated via the integration method and respiration rate (reported in Chapter 6). Original result: $r_{(28)}$=0.15, *p*=.434, BF=0.19. Re-analysis: $r_{(24)}$=0.22, *p*=.292, BF=0.26. No difference to interpretation of data made.

APP10.6.2.3. Chapter 6: 1 participant excluded.

Here, the following re-analysis was carried out (no differences to interpretation of data were made133):

35. Correlation between self-report measures of task-related difficulty. Original result: $r_{(28)}$=-0.11, *p*=.551, BF=0.23. Re-analysis: $r_{(27)}$=-0.15, *p*=.428, BF=0.26.

36. Correlation between self-report measures of task-related frustration. Original result: $r_{(28)}$=-0.06, *p*=.737, BF=0.21. Re-analysis: $r_{(27)}$=-0.11, *p*=.585, BF=0.23.

133 Note that analyses pertaining to cardio-respiratory data are reported in previous sections associated with the Study for which relevant exclusions were made.

37. Correlation between mean pupil diameter across all trials within the stop context. Original result: $r_{(28)}$=0.02, *p*=.912, BF=0.2. Re-analysis: $r_{(27)}$=0.04, *p*=.829, BF=0.2.

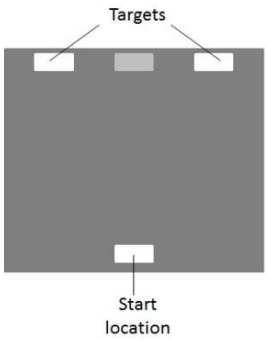
38. Correlation between mean pupil diameter across signal trials within the stop context. Original result: $r_{(28)}$=0.04, *p*=.851, BF=0.2. Re-analysis: $r_{(27)}$=0.03, *p*=.859, BF=0.26.

39. Correlation between mean pupil diameter across no-signal trials within the stop context. Original result: $r_{(28)}$=0.01, *p*=.943, BF=0.19. Re-analysis: $r_{(27)}$=0.06, *p*=.769, BF=0.21.

APP10.6.3. Task instructions

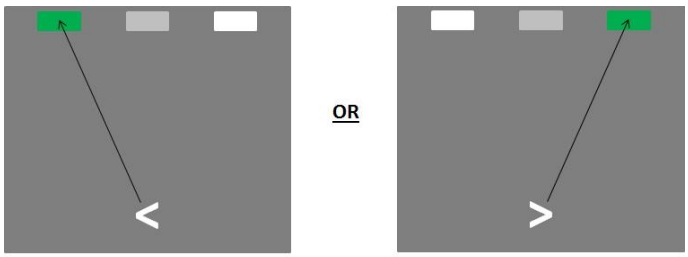
Tracking- Go- Continuous

You will be presented with rectangles on a screen. The bottom rectangle is the start location and the upper white rectangles are targets. You will be using the mouse to respond to this task.



At the beginning of each trial, position the cursor at the centre of the start location and make sure you have sufficient desk space to fully extend your arm. When ready to start the trial you must click the mouse.

The start location will turn from white to grey for a short time before being replaced by an arrow. Your task is to move the cursor to the corresponding target as **fast and as accurately** as possible.



Ensure you make one smooth continuous movement towards the target and that you do not stop your movement before reaching the target.

To be accurate, all movements must reach the target and be in must be in correct direction of the target.

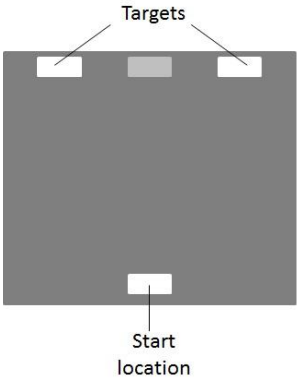
The target will turn green once the cursor reaches it. Please hold the position of the cursor within the target until the start location reappears.

The cursor can then be repositioned and the mouse clicked before the start of the next trial.

Tip: to improve accuracy it is a good idea to aim the movement of the cursor towards the centre of the target.

Tracking- Go- Discrete

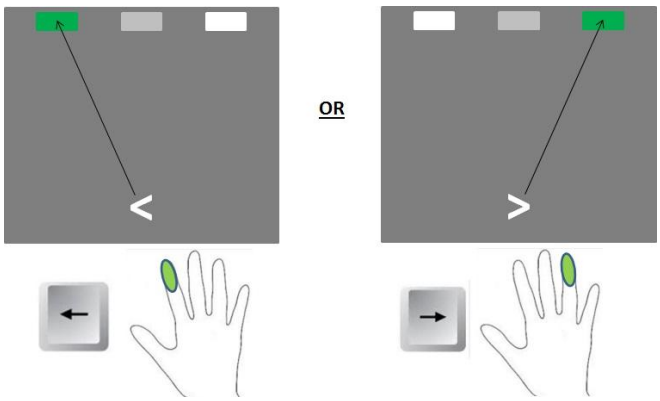
You will be presented with rectangles on a screen. The bottom rectangle is the start location and the upper white rectangles are targets. You will be using the arrow keys on the keyboard to respond to this task.



The start location will turn from white to grey for a short time before being replaced by an arrow. Your task is to move the cursor to the corresponding target as **fast and as accurately** as possible.

If the arrows is pointing left press '←' using your right index finger.

If the arrow is pointing right '→' using your right ring finger.



Ensure you make one smooth continuous movement towards the target and that you do not stop your movement before reaching the target.

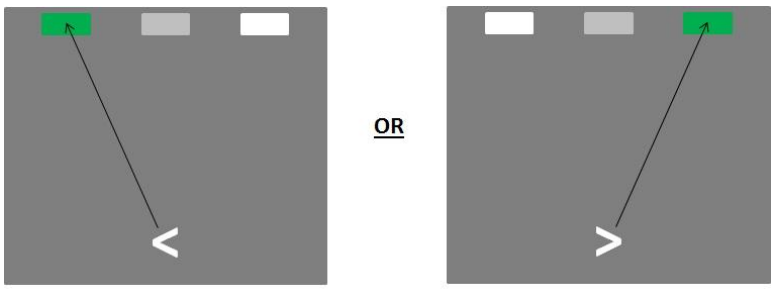
To be accurate, all movements must reach the target and must be in correct direction of the target.

The target will turn green once the cursor reaches it. The start location will reappear for 1 second before the start of the next trial.

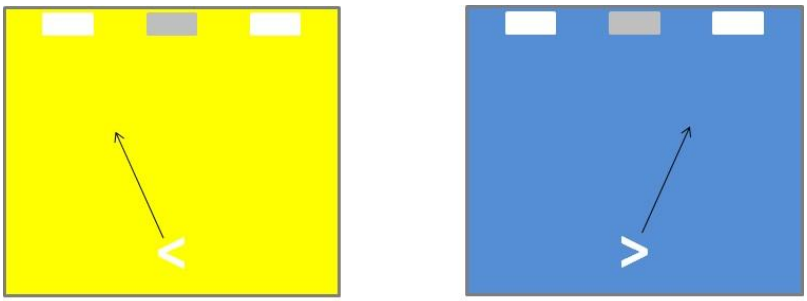
Tracking- Stop- Continuous

At the beginning of each trial, position the cursor at the centre of the start location and make sure you have sufficient desk space to fully extend your arm. When ready to start the trial you must click the mouse.

The start location will turn from white to grey for a short time before being replaced by an arrow. Your task is to move the cursor to the corresponding target as **fast and as accurately** as possible.



On some occasions the grey background will change colour after a **variable delay**. You must try to **stop** moving the cursor as fast as possible. **The researcher will tell you what colour the screen will change to.**



You will not be able to predict when the background will change colour.

You must try to stop moving the cursor before you reach the target. This will be easier on some occasions than on others, but you should not slow your responses in order to stop more often.

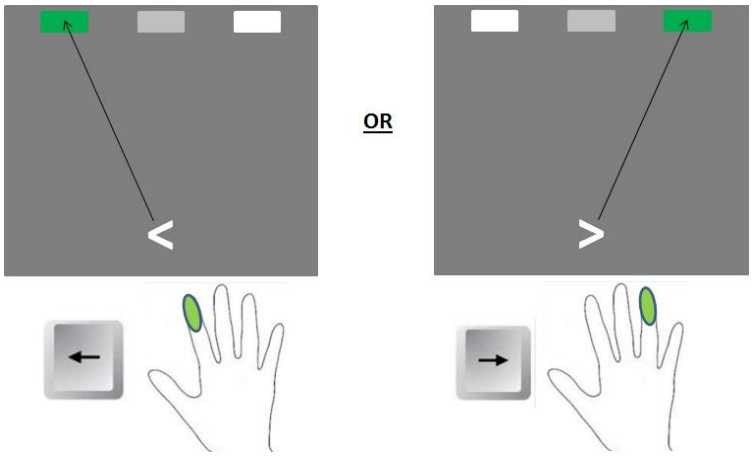
Remember not to wait for the background to change colour and to move the cursor to the targets as fast and as accurately as possible.

Tracking- Stop- Discrete

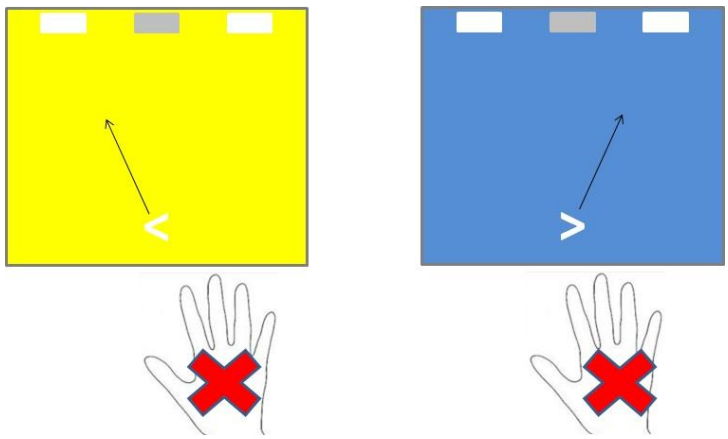
The start location will turn from white to grey for a short time before being replaced by an arrow. Your task is to move the cursor to the corresponding target as **fast and as accurately** as possible.

If the arrows is pointing left press '←' using your right index finger.

If the arrow is pointing right '→' using your right ring finger.



On some occasions the grey background will change colour after a **variable delay**. You must try to **stop** moving the cursor as fast as possible. **The researcher will tell you what colour the screen will change to.**



You will not be able to predict when the background will change colour.

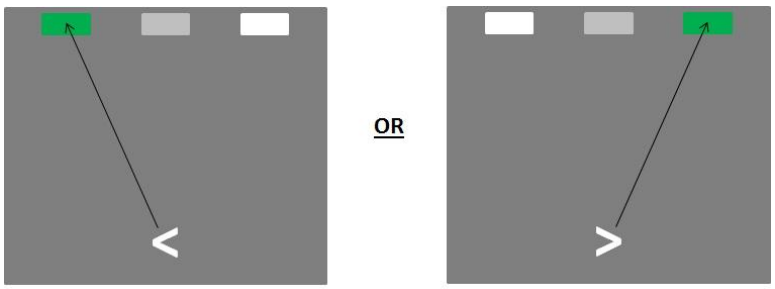
You must try to stop moving the cursor before you reach the target. This will be easier on some occasions than on others, but you should not slow your responses in order to stop more often.

Remember not to wait for the background to change colour and to move the cursor to the targets as fast and as accurately as possible.

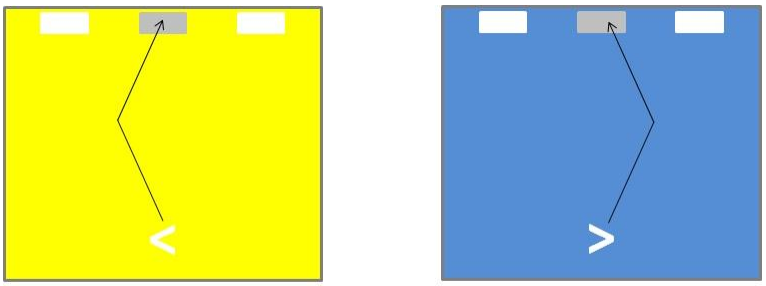
Tracking- Change- Continuous

At the beginning of each trial, position the cursor at the centre of the start location and make sure you have sufficient desk space to fully extend your arm. When ready to start the trial you must click the mouse.

The start location will turn from white to grey for a short time before being replaced by an arrow. Your task is to move the cursor to the corresponding target as **fast and as accurately** as possible.



On some occasions the grey background will change colour after a **variable delay**. You must try to **move the cursor to the upper grey rectangle** as fast as possible. **The researcher will tell you what colour the screen will change to.**



You will not be able to predict when the background will change colour.

You must try to move the cursor to the change location before you reach the target. This will be easier on some occasions than on others, but you should not slow your responses in order to be more successful.

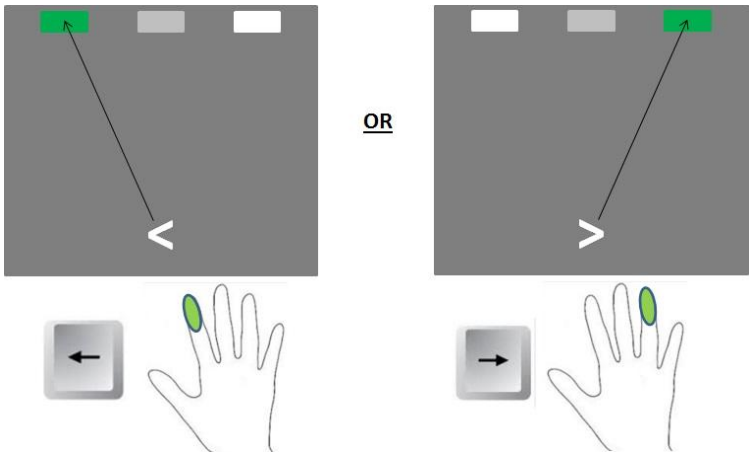
Remember not to wait for the background to change colour and to move the cursor to the targets as fast and as accurately as possible.

Tracking- Change- Discrete

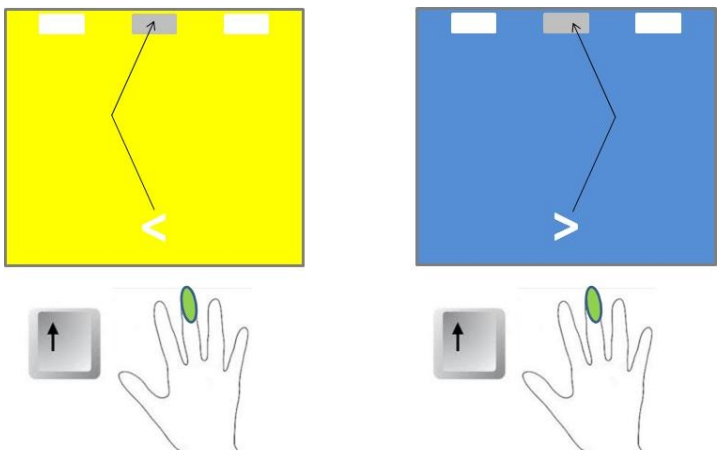
The start location will turn from white to grey for a short time before being replaced by an arrow. Your task is to move the cursor to the corresponding target as **fast and as accurately** as possible.

If the arrows is pointing left press '←' using your right index finger.

If the arrow is pointing right '→' using your right ring finger.



On some occasions the grey background will change colour after a **variable delay**. You must try to **move the cursor to the upper grey rectangle** as fast as possible by pressing the '↑' key with your right middle finger. **The researcher will tell you what colour the screen will change to.**



You will not be able to predict when the background will change colour.

You must try to move the cursor to the change location before you reach the target. This will be easier on some occasions than on others, but you should not slow your responses in order to be more successful.

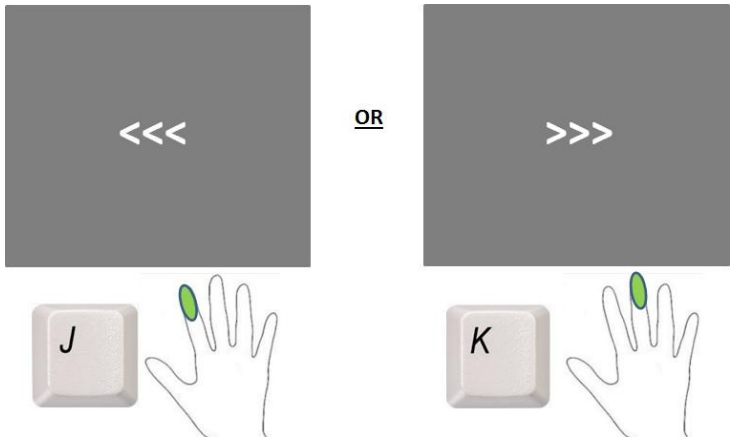
Remember not to wait for the background to change colour and to move the cursor to the targets as fast and as accurately as possible.

Stop-Signal Task

You will be presented with white arrows in the centre of the screen. You must respond to the direction of the arrows as fast and as accurately as possible.

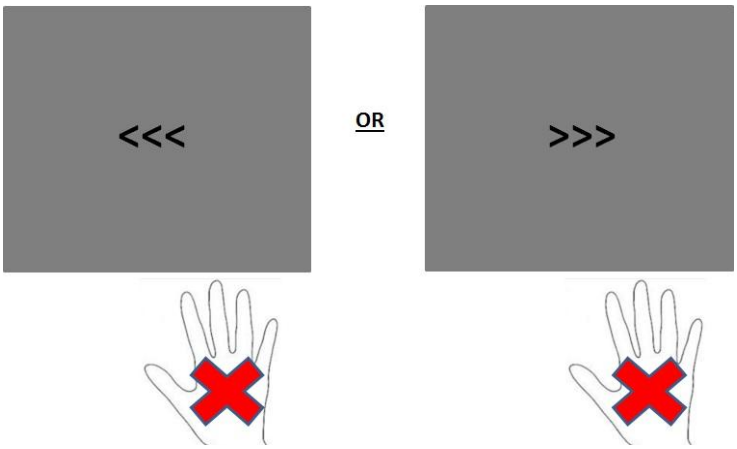
If the arrow is pointing to the left press the 'j' with your right index finger.

If the arrow is pointing to the right press the 'k' key with your right middle finger.



On some occasions the white arrow may turn black after a **variable delay.**

You must try to **stop** your response (i.e. press nothing).



You will not be able to predict when the arrow will turn black.

NOTE: at times it will be easier to stop than others, but you should not slow your responses in order to stop more often.

White crosses will be presented between arrows. You do not need to respond to these.

Remember not to wait for the arrow to turn black and to respond as fast and as accurately as possible.

On screen instructions.

Stop/change task- go only trials.

"You must move the cursor to the target location as fast and as accurately as you can.

If presented with < move the cursor to the left.

If presented with > move the cursor to the right.

Remember to hold the position of the cursor once you reach the target."

Stop/change task- stop condition.

"You must move the cursor to the target location as fast and as accurately as you can.

If presented with < move the cursor to the left.

If presented with > move the cursor to the right.

On some occasions the screen will change colour after a variable delay.

You must try to stop moving the cursor as fast as possible."

Stop/change task- change condition.

"You must move the cursor to the target location as fast and as accurately as you can.

If presented with < move the cursor to the left.

If presented with > move the cursor to the right.

On some occasions the screen will change colour after a variable delay.

You must try to move the cursor to the change location as fast as possible."

Stop-signal task.

"You must respond to the direction of the white arrows as fast as you can.

For arrows pointing left <<< press the j key.

For arrows pointing right >>> press the k key.

On some occasions the arrow will flash black.

This means you have to try to stop your response.

Remember not to slow down to be better at stopping."

APP10.6.4. Results.

Results here include analyses with outliers excluded and non-parametric tests (if applicable). The results with no outliers removed are reported in the main text. Discrepancies between results are discussed in the main text.

APP10.6.4.1. Error likelihood in the stop/change task.

7.4.1.1. Task-related difficulty and frustration in the continuous stop/change task yielded no differences ($t_{(21)}$=1.24, $p_{.025}$=.229, BF=0.44; $t_{(19)}$=0.75, $p_{.025}$=.464, BF=0.3, respectively).

7.4.1.2. Task-related difficulty and frustration in the discrete stop/change task yielded no differences ($t_{(23)}$=0.03, $p_{.05}$=.976, BF= 0.22; $t_{(22)}$=0.18, $p_{.05}$=.862, BF=0.22, respectively).

7.4.1.3. Stop and change accuracy was comparable in the continuous task (59.77±24.86% and 57.59±27.15%, respectively; $t_{(20)}$=0.68, $p_{.05}$=.61, BF=0.28).

7.4.1.4. Repeated measures ANOVA to establish whether % accuracy in the continuous stop/change task was influenced by SOD (SOD1, SOD2, SOD3) and condition, with % accuracy as the DV. There was no main effect of condition ($F_{(1,19)}$=0.08, p=.784, BF=0.2), but there was a main effect of SOD, ($F_{(1.25,23.78)}$=60.05, p<.001, Greenhouse-Geisser corrected, BF=1.24^{e+19}); whereby accuracy was found to decrease across SODs (accuracy for SOD1>SOD2>SOD, all p<.001, all BF> 132). No interaction effect was found ($F_{(2,38)}$=1.4, p=.260, BF=0.21).

7.4.1.5. Repeated measures ANOVA to establish whether % accuracy in the discrete stop/change task was influenced by SOD (SOD1, SOD2, SOD3) and condition, with accuracy as the DV. There was a main effect of condition ($F_{(1,10)}$=11.83, p=.006, BF=0.32), a main effect of SOD ($F_{(1.24,12.45)}$=307.17, p<.001, Greenhouse-Geisser corrected, BF=7.43^{e+31}), and an interaction effect ($F_{(1.23,12.26)}$=7.88, p=.018, Greenhouse-Geisser corrected, BF=5.93). Increasing SOD was found to be related to decreased accuracy (SOD1>SOD2: $p_{.05}$=.007; SOD1>SOD3: $p_{.0167}$<.001; SOD2>SOD3: $p_{.025}$<.001, all BF>113.3). The main effect of condition was driven by greater accuracy on stop relative to change signal trials. Simple main effects analysis established a disparity in accuracy between stop and change accuracy at SOD3 only ($t_{(10)}$=5.12 ,

$p_{.0167}$<.001, BF= 79.73; SOD1: $t_{(10)}$=-1.295, p=.224, BF=0.58; SOD2: $t_{(10)}$=1.49, p=.168, BF=0.71).

7.4.1.6. Paired sample t-test revealed no difference in go response accuracy in the continuous stop and change tasks ($t_{(22)}$=0.51, $p_{.05}$=.616, BF=0.25).

7.4.1.7. Repeated measures ANOVA to establish whether mean go velocity varied across the trial (when available space to move the cursor divided into thirds: beginning, middle and end) in continuous stop and change conditions. There was no main effect of condition $F_{(1,22)}$=3.48, p=.075, BF=0.28), but there was a main effect of point in the trial ($F_{(2,44)}$=100.23, p<.001, BF=7.61^{e+31}) and an interaction effect $F_{(1.970, 43.349)}$=15.05, p<.001, BF=0.42). Velocity was found to be greatest at the middle of movement, as opposed to the beginning ($p_{.025}$<.001, BF=1.36^{e+9}) or end of movement ($p_{.0167}$<.001, BF=2.23^{e+7}). No difference between the velocity at the beginning and end of movement was found ($p_{.05}$=.058, BF=1.18; although note this may be due to the removal of the initial samples from all responses). Interaction effect increased go velocity when presented in the stop relative to change conditions at the beginning ($t_{(22)}$=2.47, $p_{.025}$=.022, BF=2.6) and middle of the trial ($t_{(22)}$=2.93, $p_{.0167}$=.008, BF=7.1), but no difference was detected at the end of the trial ($t_{(22)}$=-0.39, p=.701, BF=0.23).

7.4.1.8. Repeated measures ANOVA were computed to establish whether the pre-signal velocity varied across SODs (SOD1, SOD2, SOD3) and condition (stop or change) in the continuous task. A main effect of condition was found ($F_{(1,22)}$=7.79, p=.016, BF=1.6), where pre-signal velocity was greater in the stop relative to the change task. Pre-signal velocity was found to increase across SODs ($F_{(1.07, 23.57)}$=231.49, p<.001, BF=4.97^{e+29}; p-value for all pairwise comparisons <.001, all BF>2.34^{e+9}), but no interaction effect ($F_{(2,44)}$=1.87, p=.167, BF=0.16).

7.4.1.9. Linear regression analyses were conducted to establish whether go velocity was a good predictor of signal accuracy across the different conditions. Go velocity was found to be a good predictor across all conditions (continuous stop: $F_{(1,21)}$=33.77, $p_{.025}$<.001, R^2=.62; continuous change: $F_{(1,21)}$=27.71, $p_{.05}$<.001, R^2=.560; discrete stop: $F_{(1,19)}$=75.57,$p_{.0125}$<.001, R^2=.8; discrete change: $F_{(1,21)}$=54.56, $p_{.0167}$<.001, R^2=.72)[134] , and accuracy was found to decrease by 3.57-5.21% per pixel increase in velocity on

[134]Accuracy was found to decrease by 3.57%, 3.55% for every pixel increase in velocity in the continuous stop and continuous change tasks, respectively and 5.21% and 3.99% in the discrete stop and change tasks, respectively.

average. Importantly, this highlights the possibility that the task may not be adequate to fully appreciate the action updating abilities of particularly fast responders. Indeed, the fastest responder was found to successfully inhibit only 3.13% of stop trials and successfully adjust response trajectory on 5.21% change trials. For this participant, continuous go-velocity was on average 41.94 pixels per sample, more than double the mean go-velocity of the remaining participants (18.42±5.06 pixels per sample).

APP10.6.4.2. Recruitment of inhibition in the change condition.

7.4.2.1. A repeated measures ANOVA was conducted to establish whether there was a difference in the % of instances of slowing and stopping before a successful change response in the continuous change condition. Slowing was found to occur significantly more often than stopping ($F_{(1,17)}$=85.09, p<.001, BF=9.65^{e+7}). There was also a main effect of SOD ($F_{(1.39,1.48)}$=7.94, p=.005, Greenhouse-Geisser corrected, BF=15.8), where SOD3>SOD1, $p_{.0167}$<.001, BF=45.27; SOD 2>SOD1, $p_{.025}$=.002, BF=23.56, but no difference between SOD3 and SOD2, p=.285, BF=0.41). There was also an interaction effect $F_{(2,34)}$=4.96, p=.013, BF=2.65), and slowing was found to occur more often than outright stopping across all SODs (all p<.002, all BF>20.35).

7.4.2.2. Violations of normality assumption for the repeated measures ANOVA mentioned above warranted a non-parametric analysis. Friedman's test: X^2(5, N=24)=63.38, p<.001. Outliers removed: X^2(5, N=18)=49.96, p<.001

APP10.6.4.3. Action updating across distance.

7.4.3.1. A repeated measures ANOVA was conducted to establish whether condition and SOD influenced RTs to update (slow, stop or change) in the continuous stop/change task. There was a main effect of updating condition ($F_{(1.2,23.03)}$=30.16, p<.001, Greenhouse-Geisser corrected, BF=7.71^{e+10}), whereby RTs to stop were significantly longer than to slow ($p_{.025}$<.001) and change ($p_{.0167}$<.001) a response. There was no difference in RTs to slow or change a response (p=.85, BF=). There was also a main effect of SOD ($F_{(1.15,24.2)}$=115.83, p<.001, Greenhouse-Geisser corrected, BF=3.98^{e+14}), due to RTs decreasing

with SOD (SOD1>SOD2>SOD3, all p<.001, all BF>1.19^{e+6}). No interaction effect was observed ($F_{(1.46,30.61)}$=1.68, p=.207, Greenhouse-Geisser corrected, BF=0.09).

7.4.3.2. A repeated measures ANOVA was conducted to establish whether condition and SOD influenced RTs to update (slow, stop or change) in the discrete stop/change task. There was a main effect of updating condition, whereby change RTs were greater than stop RTs ($F_{(1,15)}$=33.33, p<.001, BF=94133.89). A main effect of SOD was found, whereby increasing SOD was associated with shorter stop and change RTs ($F_{(1.07,15.98)}$=13.43, p<.001, Greenhouse-Gesisser corrected, BF=241.67; SOD1>2:$p_{.0167}$<.001, BF=14795.8, SOD1>3: $p_{.025}$<.001, BF=57.29; SOD2>SOD3: $p_{.05}$=.016, BF=2.11). No interaction effect was found ($F_{(1.03,15.37)}$=0.74,p=.407, Greenhouse-Geisser corrected, BF=0.22).

7.4.3.3. A repeated measures ANOVA was conducted to establish whether condition and SOD influenced distances to update (slow, stop or change) in the continuous stop/change task. There was a main effect of condition ($F_{(1.031,20.621)}$=10.54, p=.004, Greenhouse-Geisser corrected, BF=.09), where distances to stop were greater than distances to slow (p<.001, BF=207365.87) and distances to change (p<.001, BF=24.55). Distances to slow a response were also greater than distances to change a response (p=.020, BF=2.81). A main effect of SOD ($F_{(1.121,22.428)}$=185.74, p<.001, Greenhouse-Geisser corrected, BF=1.65^{e+72}) revealed increased updating distance with shorter SODs (SOD1>SOD2>SOD3, all p<.001, all BF>). There was no interaction effect ($F_{(1.74,34.78)}$=0.71, p=.478, BF=.05).

7.4.3.4. A repeated measures ANOVA was conducted to establish whether condition and SOD influenced distances to update (stop or change) in the discrete stop/change task. There was a main effect of condition, where distances to change ere greater than distances to stop ($F_{(1,13)}$=21.7, p<.001, BF=1.31). A main effect of SOD $F_{(1.25,17.2)}$=81.85, p<.001, Greenhouse-Geisser corrected, BF=8.3^{e+19}), revealed shorter distances to update with increasing SOD (SOD1>SOD2>SOD3, all p<.001, all BF>2959). An interaction effect ($F_{(1.35,17.6)}$=10.59,p=.002, Greenhouse-Geisser corrected, BF=0.7) revealed that the distance to change was greater than distance to stop across all SODs (all p<.032, all BF>2.17).

APP10.6.4.4. Comparison with the stop-signal task.

7.4.4.1. Correlations between SSRT and goRT estimates with RT and distance measures from the stop conditions in the continuous and discrete stop/change task. Results are inclusive of all participants (excluding 3 participants who were found to have negative SSRTs).

Table APP10.6.7. Summary of correlations between stop signal reaction time as acquired via the classic stop signal task with distances to slow and stop in the stop conditions of the continuous and discrete stop/change tasks.

	Continuous				Discrete	
	Slow RT	Stop RT	Slow Dist	Stop Dist	Stop RT	Stop Dist
SSRT	-0.01	0.04	-0.12	-0.11	-0.12	-0.28
BF	0.23	0.23	0.26	0.25	0.26	0.46

Note. **SSRT**=stop signal reaction time in the stop signal task as estimated via the integration method; **RT**= reaction time; **Dist**=distance; **BF**=Bayes Factor. Values correspond to Pearson's correlation coefficients. All *p*-values>0.05. All degrees of freedom=19.

No correlations between go RT in the SST and go RT in the continuous task was found ($r_{(19)}$=0.19, *p*=.410, BF=0.31) or between go RT in the SST and go RT in the discrete task ($r_{(19)}$=-0.14, *p*=.538, BF=0.27).