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Registered Report

Impairment of manual but not saccadic response inhibition following acute alcohol intoxication☆

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ABSTRACT

Background: Alcohol impairs response inhibition; however, it remains contested whether such impairments affect a general inhibition system, or whether affected inhibition systems are embedded in, and specific to, each response modality. Further, alcohol-induced impairments have not been disambiguated between proactive and reactive inhibition mechanisms, and nor have the contributions of action-updating impairments to behavioural 'inhibition' deficits been investigated.

Methods: Forty Participants (25 female) completed both a manual and a saccadic stop-signal reaction time (SSRT) task before and after a 0.8 g/kg dose of alcohol and, on a separate day, before and after a placebo. Blocks in which participants were required to ignore the signal to stop or make an additional 'dual' response were included to obtain measures of proactive inhibition as well as updating of attention and action.

Results: Alcohol increased manual but not saccadic SSRT. Proactive inhibition was weakly reduced by alcohol, but increases in the reaction times used to baseline this contrast prevent clear conclusions regarding response caution. Finally, alcohol also increased secondary dual response times of the dual task uniformly as a function of the delay between tasks, indicating an effect of alcohol on action-updating or execution.

Conclusions: The modality-specific effects of alcohol favour the theory that response inhibition systems are embedded within response modalities, rather than there existing a general inhibition system. Concerning alcohol, saccadic control appears relatively more immune to disruption than manual control, even though alcohol affects saccadic latency and velocity. Within the manual domain, alcohol affects multiple types of action updating, not just inhibition.

1. Introduction

Impaired behavioural control is strongly linked with the development of substance abuse disorders such as alcoholism (e.g., Lawrence et al., 2009; Nigg et al., 2006). Moreover, the acute effects of intoxication on inhibitory control in healthy volunteers can produce a feedback loop making further consumption likely (Weafer and Fillmore, 2008). However, the nature of such acute effects on response inhibition – for example the extent to which they are general or modality specific – remain relatively little understood.

Most reports of alcohol disrupting inhibitory control in healthy volunteers have employed the go/no-go task (Mulvihill et al., 1997; Weafer and Fillmore, 2008), cued go/no-go task (Marczinski and Fillmore, 2003; Weafer and Fillmore, 2012) and the stop signal reaction time task (Caswell et al., 2013; de Wit et al., 2000; Dougherty et al., 2008; Fillmore and Vogel-Sprott, 1999; Gan et al., 2014; Loeber and Duka, 2009; McCarthy et al., 2012; Nikolaou et al., 2013; Ramaekers and Kuypers, 2006; Reynolds et al., 2006). Although there exist reports where alcohol had no significant effect (Rose and Duka, 2008, 2007), taken together, these studies suggest that even a relatively small dose of alcohol (e.g., 0.45 g/kg) normally increases the number of commission errors in the go/no-go task or slows the manual stop signal reaction time (SSRT) in the stop signal task.

In order to extrapolate from these manual tasks, one must assume that they represent all response inhibition processes. However, response control mechanisms may be enmeshed in planning networks for each kind of response, and thus may be independent for different domains (e.g., Roberts et al., 2011). Within the field of response control, there are studies on both manual inhibition and eye movement ('saccade') inhibition and there are hints that alcohol may not impair eye

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movement inhibition in the same way as manual inhibition. If this were true, it would both provide a means to distinguish and examine different inhibition networks and also show that the effect of alcohol has more specificity than often assumed.

One of the most widely used eye movement tasks is the anti-saccade task, which has been an important bridge between human research and monkey neurophysiology. Participants make either a reflexive saccade to a target location (pro-saccade) or a saccade to the opposite location (anti-saccade) inhibiting their reflexive response. While two studies found alcohol to increase anti-saccade error rates in either head-injured participants (Crevits et al., 2000; blood alcohol levels between 1.89 and 3.84 g/l) or healthy participants (Marinkovic et al., 2013; alcohol dose 0.6 g/kg for males and 0.55 g/kg for females), two studies found no effect (healthy participants, Blekher et al., 2002; breath alcohol concentration 80 mg/dl; Vorstius et al., 2008; breath alcohol concentration 65 mg/dl). Counter-intuitively, two studies even found decreases in error rates (healthy participants, Khan et al., 2003; blood alcohol concentration 0.08%; Vassallo et al., 2002; blood alcohol concentration 0.044%), which may be due to alcohol attenuating the reflexive response rather than the inhibitory control process (Fillmore and Weafer, 2013). Similarly, in a saccade interference task in which saccade latency is slowed by large interfering stimuli, alcohol produced no significant effect (healthy participants, Abroms et al., 2006). In a third task − the delayed ocular return task − moderate doses of alcohol (0.45 g/kg and 0.65 g/kg) in healthy participants did increase the number of premature saccades (a failure of inhibition; Abroms et al., 2006; Weafer and Fillmore, 2012), but this impairment did not correlate with the impairment to their manual task (cued go/no-go), indicating independent systems (Weafer and Fillmore, 2012). However, as these authors pointed out, these eye movement tasks are not directly comparable to the commonly used manual tasks (go/no-go and stop signal) – eye movement versions of these tasks have not been studied with alcohol. Therefore, the reported differences between domains may reflect differing attentional requirements across the different tasks, for example, rather than differences in response inhibition itself.

Here, we set out to measure the effects of alcohol on manual and eye movement stop signal tasks (also called saccade countermanding) – a paradigm allowing a direct comparison. Theoretical and computational models of stopping behaviour have been cross-fertilized by both human manual response distributions and single-cell recordings of saccade countermanding in macaques (for a review see Schall and Boucher, 2007; Verbruggen and Logan, 2008). Boucher et al. (2007) conducted a stop signal task that required both ocular and manual responses simultaneously. Saccade SSRTs were 100 ms to 150 ms shorter than manual SSRTs (consistent with shorter latencies in general) but positively correlated with them. Relatedly, Leung and Cai (2007) reported a common ventro-lateral prefrontal cortex network for response inhibition in both manual and ocular domains (though differential modality-specific networks were also identified). Saccadic SSRT has not been assessed under alcohol intoxication, but anaesthetics appear to cause impaired inhibition through increased SSRT (in healthy participants, Khan et al., 1999; Nouraei, 2003). These anaesthetics (isoflurane and sevoflurane) have similar neuropharmacological actions to alcohol, i.e., potentiation of GABAergic activity at $GABA_A$ receptors and the blockade of glutamatergic NMDA receptors (Farrant and Nusser, 2005; Nishikawa and Harrison, 2003).

Our first aim was to test whether alcohol affects saccade countermanding; i.e., whether saccadic SSRT is lengthened during acute intoxication. Our second aim was to test whether any effect of alcohol on saccadic countermanding is similar or different to alcohol-induced impairment of manual countermanding (which we expect to replicate). Similar effects would be consistent with a common motor inhibition network, while different effects would suggest specificity in the inhibition mechanisms vulnerable to alcohol intoxication.

Our third aim was to unpack alcohol-induced impairment of manual countermanding (and saccadic SSRT if it occurs) into separable contributions from attentional processes and different types of inhibitory processes. Previous studies have assumed that any lengthening of SSRT must reflect an impairment to inhibition, but have not further specified the type of inhibition involved. Both reactive and proactive inhibition are forms of behavioural control which contribute to stop signal performance (e.g., Aron, 2011; Chikazoe et al., 2009; Hu and Li, 2012; Zandbelt et al., 2013). The effect of proactive control, in which participants adjust their behaviour in anticipation of trials where they might need to stop, can be assessed by comparing go trials in blocks where stopping is occasionally required to go trials in blocks where stopping is never required (the signal is ignored; Aron, 2011). This comparison is available in one previous alcohol study, but while proactive inhibition was numerically reduced under alcohol, the effect was not statistically significant (Nikolaou et al., 2013) leaving open either possibility − that alcohol may influence only reactive inhibition, or may influence both proactive and reactive inhibition.

Moreover, even though studies of alcohol and stopping performance have assumed that lengthened SSRT represents impaired inhibition (of some kind), the extent to which changes in SSRT reflect specifically inhibitory mechanisms at all has been debated. The task also requires attention to the signal and may involve non-inhibitory action updating processes (e.g., Verbruggen et al., 2010). It is possible that the previously measured effects of alcohol reflect these processes rather than impaired inhibition. Such contributions can be assessed with blocks where the 'signal' instructs an additional response, rather than a stop, since in these trials attention to the signal and action updating are still required, but response inhibition is not. Further, in these dual response trials, the relative effects on attention and action updating can be disentangled by applying the 'locus of slack' methodology to the psychological refractory period (see Pashler, 1994; Verbruggen et al., 2010).

2. Methods

2.1. Participants and screening

2.1.1. Sample size

The sample size was determined using a stopping rule based on the Bayes factor for our most important comparison, which also likely has the smallest effect size (see Section 2.8.2). The first look was at 16 participants, and participants were added in sets of 4 (see counterbalancing, section 2.3) until there was substantial evidence for either the experimental hypothesis ($B > 3$) or the null hypothesis ($B \leq 0.33$) (Dienes, 2011) or the maximum sample size (40) was reached, as occurred. The study was approved by the School of Psychology Ethics Committee at Cardiff University.

2.1.2. Recruitment and screening

Participants were undergraduate, postgraduate and staff volunteers at the School of Psychology, Cardiff University, meeting the following pre-registered inclusion criteria: body mass index (BMI) within the range 18–28 (as McCarthy et al., 2012), self-reported alcohol use below 'alcohol dependence' (less than 16 on both the Alcohol Use Disorder Identification Test, AUDIT; Babor et al., 2001, and the Severity of Alcohol Dependence Questionnaire, SADQ; Stockwell et al., 1983); experience of consuming 6 UK units (1 unit = 8 g ethanol) of alcohol in one session on at least 6 occasions within the past year (i.e., at least once every other month on average); breath alcohol concentration (BrAC) of 0 µg/100 ml on arrival, confirmation of 24 h abstinence of alcohol, 1 week abstinence of illicit drug use and 4 h fasting; self-reportedly not pregnant; no allergic reaction to alcohol (or Orangina) or clinically relevant self-reported anxiety or depression (measured by the Hospital Anxiety and Depression Scale, HADS; Zigmond and Snaith, 1983, cut-off score of > 11 on either scale); no taking of neuroactive medication or medication that may be affected by alcohol. Participants also provided information about average alcohol consumption over the past month and completed the Mother/Father-Short Michigan

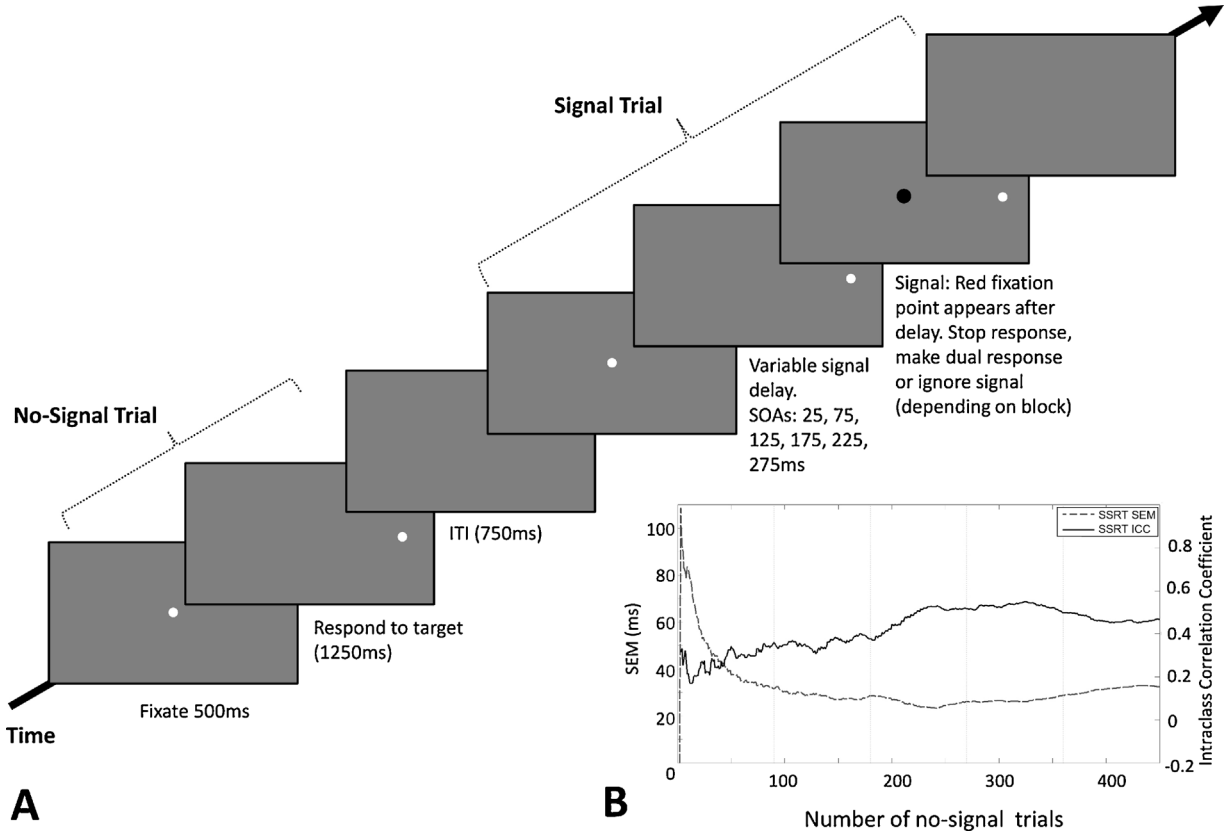

Fig. 1. Schematic of task design and reliability estimates of SSRT by no-signal trial numbers **A:** Task design for both manual and saccade tasks. The variable delays between target onset and signal are 50, 100, 166.67, 233.33, 316.67 and 400 ms (e.g., Boucher et al., 2007). Before first fixation participants were told which block they were completing (STOP, IGNORE or DUAL). **B**. Estimation of trial numbers required to assay SSRT − The expected reduction in SEM and increase in intra-class correlation coefficient (ICC) of the SSRT as more trials are included, estimated from subsampling previous data (Hedge et al., 2017.) investigating test-retest reliability with 47 participants. These asymptote at around 200 no signal trials (i.e., about 60–70 STOP trials), reaching an ICC of between 0.4 and 0.5. To be conservative, r = 0.4 is used for power calculations below.

Alcoholism Screening Test (M/F-SMAST) and Family Tree Questionnaire (FTQ) to assess family history of alcohol-related problems. See section 2.5 for pre-registered, task-related exclusion criteria. Participants were also able to withdraw themselves and their data for any reason or without giving a reason.

2.2. Tasks

Over two testing days (alcohol and placebo) participants completed separate blocks of each experimental task (outlined below) in a counterbalanced order, in sessions before and after drink manipulation.

2.2.1. Manual response stop signal task (STOP block)

A white central fixation point (0.4° or 15 pixels square) was presented on a mean luminance grey background for 500 ms, and then replaced by a peripheral target 12° from centre, of same colour and size as the fixation point, to the left or right with equal frequency in a randomised order (Fig. 1A). Participants made speeded responses with right or left index fingers to the location of the target before it extinguished (after 1250 ms) at the end of the trial (total trial length 2500 ms). On 25% of trials a red central fixation point appeared (the 'signal') at a variable delay following the target (50, 100, 166.67, 233.33, 316.67 or 400 ms e.g., Boucher et al., 2007), indicating that the response should be withheld. There were 12 trials for each signal delay randomly shuffled, and thus 72 stop signal trials with 216 no signal trials, in 4 blocks of 72 trials (with the opportunity for a break between each). Previous investigations of test-retest reliability in our group indicate that this is the optimal number of trials, since the standard error in measurement (SEM) of the SSRT asymptotes at approximately 200 no-signal trials (Fig. 1B). Participants were told not to wait for the signal before responding and that for signal trials some would be easier to inhibit than others due to the varying signal delay. Before the first block there were 32 training trials containing 8 stop-signal trials. The second 16 trials of the 32 were a criterion test, using only the shortest signal delay (easiest condition), which were repeated until the participant made $\leq 2/12$ errors on no-signal trials and $\leq 1/4$ errors on signal trials within 8 iterations of this criterion test. If the participant failed to achieve this level of performance within 8 iterations the participant was excluded (see section 2.5.1). On day 2, we also applied the 16-trial criterion test.

2.2.2. Manual signal-Ignore task (IGNORE block)

Using identical stimuli to that explained above (Section 2.2.1), participants completed 4 blocks of 72 trials with the instruction (given verbally and written) to ignore the signal and continue to make a correct button press response. There was also training at the start of the first IGNORE block as described above.

2.2.3. Manual dual task (DUAL block)

Using identical stimuli and training to that explained above (section 2.2.1), participants completed 4 blocks of 72 trials with the instruction (given verbally and written) to complete their response to the first target and make an additional speeded response if the 'signal' appears (using the thumb of either hand; as in Verbruggen et al., 2010).

2.2.4. Saccade stop signal task (Saccade countermanding − STOP block)

The same protocol was used as in the manual task, but participants made saccades to the left and right targets. On signal trials participants were instructed to inhibit these saccades. Gaze was monitored using a Tobii TX300 eye tracker at a binocular sampling rate of 300 Hz.

Participants were seated approximately 60 cm from a 51 × 29 cm (23 inch) monitor (as also in the manual task), and performed a standard gaze calibration procedure at the start of each block.

2.2.5. Saccade signal ignore task (IGNORE block)

As for the manual task 4 blocks of the same protocol were completed under the instruction to ignore the signal and to continue to saccade to the target. For saccades, there is no precedent for the dual task condition, and no easy equivalent of the manual dual response. Thus, we did not attempt to run a saccade dual response condition.

2.3. Procedure

2.3.1. Overall procedure

Participants completed a placebo day and alcohol day, consisting of a 'pre-drink' session (all tasks, 1 h), the drink challenge (30 mins), 15 mins rest and then a 'post-drink' session (all tasks, 1 h). For each participant testing sessions were at the same time of day 1 week apart. For successful recruitment of participants there was a flexibility allowance in this time gap (5–14 days gap). This also ensured sufficient washout between sessions. Testing days were booked in advance with participants to ensure this timeframe was adhered to. Participants provided informed consent and completed all the screening questionnaires and confirmation of inclusion criteria on arrival. Participants also completed the subjective high assessment scale (SHAS; Schuckit, 1980) and biphasic alcohol effects scale (BAES; Holdstock and de Wit, 1998) before each task session. Breathalyser measurements were taken before each task session and between every two blocks (approximately every 10 min). Once the tasks were complete participants completed the SHAS and BAES again. Participants then remained in the laboratory for 2 h and until BrAC was below 36 μg/100 ml.

Participants were given automated feedback and information about the number of remaining blocks after each block, and the instruction to 'respond as fast as possible whilst minimising errors' was repeated, along with the information that some trials are meant to be difficult and some errors are expected.

2.3.2. Counterbalancing

The order of placebo/alcohol and manual/saccade modalities was counterbalanced across participants, which is why participants were added in groups of 4 to satisfy the Bayesian stopping rule. We did not counterbalance modalities across sessions because we were subtracting/comparing data between sessions, not averaging over sessions (averaging over different task orders reduces effects of learning or fatigue, but subtracting data using different task orders introduces effects of learning or fatigue). Within each modality, block order (STOP, IGNORE, DUAL for manual or STOP, IGNORE for saccades) was palindromic with the local order counterbalanced across participants (we did not anticipate that this would create important confounding effects, but we did monitor it if the stopping rule meant that a complete set was not completed). The total time for all blocks was approximately 1 h.

2.4. Alcohol challenge

The alcohol dose was 0.8 g/kg of body weight for males and 90% of this for females (due to differences in body water content, Brumback et al., 2007; Sutker et al., 1983). The appropriate dose of vodka (40% alcohol by volume) was made up to a 500 ml solution with the carbonated citrus drink Orangina and divided into 10 equal aliquots of 50 ml each, and was consumed one every 3 min (Rose and Duka, 2008). This dose and administration time was anticipated to give a peak blood alcohol concentration (BAC) of 0.1% (equivalent to 44 μg/100 ml BrAC) at 30 min after the last drink had been consumed.

The placebo drink comprised ten 50 ml aliquots of Orangina with the rim of each glass sprayed with vodka and a few drops of vodka (< 5 ml) floated on top the drink to give the initial taste and smell of alcohol (Rose and Duka, 2008). A double-blind procedure was employed where both the experimenter and participant were blind to drink condition. Drinks were prepared by an experimenter not involved with data collection prior to each testing session. This experimenter later decoded datasets for group level data analyses. This was to reduce any unconscious bias induced by the experimenter collecting data. In any alcohol study, it is likely that many participants would detect which drink contains alcohol as they are familiar with its effects, but alcohol expectancy effects are not likely to mediate alcohol induced impairments to inhibitory control (Caswell et al., 2013), and are very unlikely to produce differential performance in manual vs. saccadic tasks.

2.5. Initial data processing and exclusion criteria

2.5.1. Pre-drink exclusion

Participants were not allowed to proceed to the drink challenge and post-drink session if they failed to pass the criterion test within 8 iterations, their pre-drink error rate on no-signal trials or IGNORE trials was above 10% or their mean RT was above 600 ms, or inhibition failure rate on STOP trials was above 50% for the easiest condition (50 ms delay − this would indicate they were not fully attempting to stop) or below 50% for the hardest condition (400 ms delay − this would indicate they were not fully attempting to go before the signal occurs). This ensured the inhibition function (proportion of failed inhibitions by signal delay) crossed 50%.

2.5.2. Post-drink exclusion

Participants were excluded from further sessions if they did not complete the alcohol challenge as specified, or if they did not complete any session (e.g., due to adverse effects of alcohol, or self-withdrawal). For participants with complete data for all sessions, their data was excluded from further analysis if post-drink error rates on no-signal trials or IGNORE trials were above 20%, their inhibition function did not cross 50%, or mean RT for no-signal trials in all conditions exceeded 3SDs from the group mean in any session. For the dual task condition data was not used if error rates were above 20% or grouping of responses was detected on more than 10% of dual response trials (defined as the second response within 50 ms of the first).

2.5.3. Trial analysis and exclusion

Eye movement data was processed following standard procedures (e.g., Bompas and Sumner, 2011). Briefly, accepted saccades were detected using a velocity criterion of greater than 35°/s, an acceleration of 6000°/s2 trials, and an amplitude of at least 6° (halfway to the target). Trials were excluded if they showed loss of tracking or blinks (visible on the eye-trace as large deflections with temporary loss of tracking in the middle) in the period 100 ms before target onset to 100 ms after saccade offset, or small saccades (under 6°) from 100 ms before target onset until the first 6° saccade. All eye movement data were plotted and visually inspected to check the algorithm's classification, as is standard procedure for eye tracking experiments (the inspector was blind to condition, so could not bias results). Visual inspection ensured that the algorithm had detected appropriate saccades, not noise, had correctly identified saccade start points, and ensured that trials with blinks, tracking loss or fixation loss were removed.

For both manual and saccadic responses, RTs less than 80 ms (anticipations) or greater than 3 SD from the mean for that participants' session were removed from further analyses. SSRT for each task, time and drink condition were calculated using the integration method (Logan, 1994; Logan and Cowan, 1984).

2.6. Statistical approach

We adopted both a traditional approach using null hypothesis significance testing and a Bayesian approach. Analyses of variance (ANOVA) and *t*-tests were conducted where appropriate but we also

calculated the Bayesian equivalents. The conventional significance tests provide familiarity and ease of comparison with previous literature, whereas the Bayesian statistics provide evidence for both the null hypothesis and the alternative hypothesis (see Dienes, 2011). In the majority of cases a 2 (Drug: Alcohol, Placebo) by 2 (Time: Pre-Drink, Post-Drink) within-subjects ANOVA was conducted on the relevant data (e.g., SSRT, saccade velocity). For the Bayesian equivalent, the data were collapsed as follows to derive a difference score: the relative change from pre-drink to post-drink was calculated for placebo and alcohol separately (post-drink score minus pre-drink score divided by pre-drink score), then the difference between the placebo and alcohol relative changes was calculated. A Bayesian test was conducted on these difference scores using the default JZS prior described by Rouder et al. (2009). Substantial evidence for the null or alternative was considered as Bayes factors of < 0.33 or > 3 respectively (Jeffreys, 1961 as cited in Dienes, 2011).

2.7. Confirming expected effects

2.7.1. Alcohol intoxication: outcome-neutral manipulation check

To confirm intoxication, 2 (Drug: Alcohol, Placebo) by 2 (Time: Pre-Drink, Post-Drink) within-subjects ANOVAs and equivalent Bayesian tests were conducted on scores from the BAES and SHAS subjective measures of intoxication. A further 2 × 2 within-subjects ANOVA and equivalent Bayesian test was conducted on peak saccade velocity (slowing of velocity is a robust measure of alcohol intoxication; Lehtinen et al., 1979) from the no-signal trials across all blocks of the saccade task. A Drug x Time interaction in at least one of these measures was required to confirm intoxication. In our recent study with the same alcohol protocol (Campbell et al., 2014), all three showed clear effects with only 13 (questionnaires) or 14 (saccades) participants ($F(1.12) = 35$, $p < 0.001$; $F(1.12) = 28$, $p < 0.001$; $F(1.13) = 16$, $p = 0.002$).

2.7.2. Alcohol increasing manual SSRT

A 2 (Drug: Alcohol, Placebo) x 2 (Time: Pre-, Post-Drink) within-subjects ANOVA and complimentary Bayesian test was conducted on the mean SSRTs from each participant. Table 1 shows previously published effect sizes for the comparison of manual SSRT between alcohol and placebo conditions. Note that these come from a variety of designs, also with different numbers of trials. As Fig. 1B indicates, a stable estimate of SSRT requires at least 200 trials, and the most comparable design to ours (entirely within-subjects with pre- and post-drink conditions, in a standard laboratory, not during MRI scanning) is that of de Wit et al. (2000) with an ηp2 = 0.26. Table 2 shows the minimum effects we were able to detect for our sample size of 16–40.

Table 2
Range of effect sizes that could be detected at 4 possible sample sizes for a 2 × 2 within-subjects ANOVA at α = 0.05, 1-β = 0.9, correlation between repeated measures = 0.4 (see Fig. 1 B for explanation). These detectable effect sizes compare favourably to previously found effect sizes (Table 1).

Sample Size	*Minimum detectable effect size (η_p^2)*
16	0.13
24	0.09
32	0.06
40	0.05

2.8. Pre-registered analyses of interest

2.8.1. Does alcohol increase saccadic SSRT?

For saccadic SSRT, as for manual SSRT, we conducted a 2 (Drug: Alcohol, Placebo) x 2 (Time: Pre-, Post-Drink) within-subjects ANOVA and comparable Bayesian test. The range of effect sizes detectable was the same as those detailed in Table 2. We are not aware of any previously published data for this comparison.

2.8.2. Does alcohol affect manual SSRT to a greater extent than saccadic SSRT?

Because we were equally interested in the null possibility (similar alcohol effects for manual and saccadic SSRT), we collapsed the data to enable a Bayes factor to be calculated. Relative change in SSRT from pre-drink to post-drink was calculated for alcohol and placebo for each task modality. The difference in these relative changes was calculated between alcohol and placebo for each response modality. This should quantify the effects of alcohol on each modality separately. The differences and similarities between how the modalities are affected can then be quantified using a Bayes factor (as Rouder et al., 2009) applied to the difference between modality-specific measures. Substantial evidence for the null hypothesis ($B \leq 0.33$) or experimental hypothesis ($B \geq 3$) would allow us to conclude whether the effect of alcohol on SSRT across response modalities was similar or different. This Bayesian inferential approach permits sequential sampling to establish participant numbers. To decide the minimum ('first look') sample size of 16, we similarly used half the expected manual effect size from de Wit et al. (thus ηp2 = 0.13 or f = 0.39, α = 0.05, 1-β = 0.90, correlation between variables = 0.4) for a 2 (Drug: Alcohol, Placebo) x 2 (Response: Saccade, Manual) within-subjects ANOVA. Maximum sample size was similarly set by using half the smallest published effect size for this

Table 1
Previously published studies comparing manual SSRT between alcohol and placebo conditions.

Study	*Alcohol to Placebo Comparison*	*Pre-drink/baseline condition*	*N*	*Number of go trials*	*Ratio Go:Stop*	*Maximum Alcohol Dose*	*Effect Size*
de Wit et al. (2000)	Within	Yes	17	192	75:25:00	0.8 g/kg	$\eta_p^2 = 0.26$
Reynolds et al. (2006)	Within	No	24	Not Stated	75:25:00	0.8 g/kg	$\eta_p^2 = 0.30$
Loeber and Duka (2009)	Between	Yes	32	240	75:25:00	0.8 g/kg	Time x Group Interaction $\eta_p^2 = 0.11$ Post-hoc pre vs post alcohol: Cohen's $d_z = 0.91$
McCarthy et al. (2012)	Within	No	29	Not Stated	Not Stated	0.72 g/kg	$\eta_p^2 = 0.12$
Caswell et al. (2013)	Between	No	48	90	75:25:00	0.8 g/kg	$\eta_p^2 = 0.16$
Nikolaou et al. (2013)	Between (fMRI)	Yes	42	120	75:25:00	0.8 g/kg	Time x Group Interaction: $\eta_p^2 = 0.156$ High dose vs placebo: Cohen's d = 0.93
Gan et al. (2014)	Within (fMRI)	No	50	320	80:20:00	0.6 g/kg	Cohen's $d_z = 0.63$

interaction of interest (regardless of within/between design or trial numbers; ηp2 = 0.055; see Table 1). This gave 38, but due to counterbalancing requirements participants were run in groups of 4, so the maximum sample was set to 40. We used the contrast between alcohol effects on manual and saccadic SSRT to set our sample size since this was our most important question.

2.8.3. Does the alcohol-Induced effect on manual SSRT correlate with the alcohol-Induced effect on saccade SSRT?

If alcohol affected both manual and saccadic SSRT, we planned to test whether these effects were correlated across participants. This took the form of a Pearson's correlation and its complementary Bayesian equivalent described in Wetzels and Wagenmakers (2012).

2.8.4. Does alcohol affect proactive inhibition?

To confirm an effect of proactive inhibition without alcohol in each modality, we compared mean latency in no-signal trials within STOP blocks with mean latency from no-signal trials in IGNORE blocks across pre-drink conditions using dependent samples *t*-tests and the Bayesian equivalent. We expected a large effect size, as in the data of Nikolaou et al. (2013); note that this analysis relied only on no-signal trials, which are 3 times more numerous than signal trials. For converging evidence, manual DUAL and STOP blocks were compared in the same way. Then, to investigate the effect of alcohol, a 2 (Time: pre-, post-drink) x 2 (Drug: placebo, alcohol) ANOVA and a complementary Bayesian test compared the latency differences between STOP and IGNORE no-signal trials. Detectable effect sizes were those in Table 2.

2.8.5. Does alcohol affect action updating or attentional processing?

Following the logic of Verbruggen et al. (2010), if the effect of alcohol on SSRT is partly due to impairments to attention or action updating, then alcohol was also predicted to affect the secondary response in the DUAL blocks, the dual reaction time 2 (DRT2). This was assessed with 2 (Time: pre-, post-drink) x 2 (Drug: placebo, alcohol) ANOVAs for the RTs and error rates in the DUAL condition signal trials and the equivalent Bayesian test. Further, attentional vs action updating effects can be distinguished using the dependency of the secondary response RTs on signal onset asynchrony (SOA); following the logic set out by Verbruggen et al. (2010) and Maizey et al. (2013), an increase in the alcohol-induced deficit on secondary RT with signal delay would imply that the deficit has been absorbed into the bottleneck at short SOAs (i.e., the psychological refractory period; PRP, see Fig. 2A). This would imply that the deficit has occurred pre- rather than post-bottleneck, suggesting an effect of alcohol on perceptual or attentional stages of processing. However, if the alcohol-induced deficit is constant across SOAs then it is likely to have occurred post-bottleneck and can be attributed to deficits in updating of action plans (see Fig. 2B). With 16 participants and a 2 × 2 x 6 within-subjects ANOVA design we could detect an effect size of ηp2 = 0.04 (α = 0.05, 1-β = 0.90, correlation between variables = 0.4, assuming sphericity).

2.9. Subsidiary analyses

Given possible sex differences in baseline performance of the manual stop-signal task (e.g., McCarthy et al., 2012), all analyses were conducted additionally using gender as a covariate. Furthermore, assessment of the impact of order effects of both block type and drink type were conducted for all analyses to understand whether these are impacting manual or saccadic SSRT.

2.9.1. Saccadic inhibition effect – additional analysis of potential interest

The inclusion of trials on which participants were required to ignore the stop signal allowed for the investigation of whether the saccadic inhibition effect from a visual distractor (e.g., Reingold and Stampe, 2002) was present in our data and whether it was affected by alcohol. Latency distributions from both saccades and manual responses on signal-present ignore trials were analysed for the presence, amplitude and delay of 'dips' time-locked to the onset of the signal following the procedure detailed in Bompas and Sumner (2011). In order to provide enough trials to generate good quality saccade latency distributions, data were pooled across all participants and statistical tests were not able to be conducted. There was no precedent to know the likely effect size of alcohol here, but the basic saccadic inhibition effect is very robust (N = 64 reported effects, mean r = 0.82, SD = 0.11, as calculated in Harrison et al., 2014).

2.10. Post-Hoc analyses: confirming main results with improved bayesian method

The pre-registered Bayesian approach of collapsing the 2 × 2 design down into a single *t*-test through calculating relative changes from pre- to post-drink, then taking the difference between alcohol and placebo, does not maintain the separate variances attributable to each variable. This can lead to an analysis that does not capture the appropriate

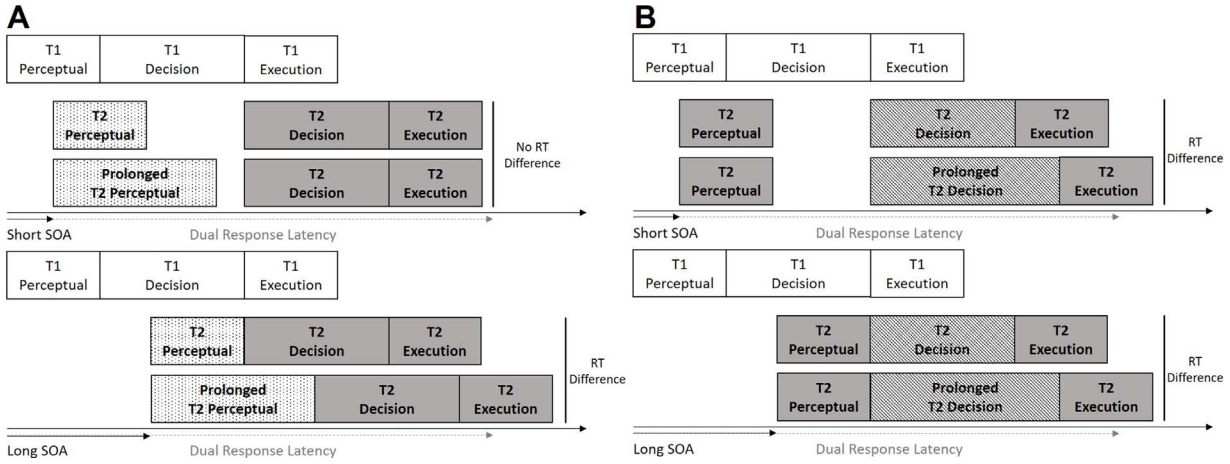

Fig. 2. Schematic representation of how alcohol may affect different stages of processing and how this would manifest in the reaction time difference according to SOA. During multiple response selection, the central decision-making stages of processing cannot be conducted in parallel creating a bottleneck of processing where the decision stage of the first response must be completed before the decision stage of the second response can start; therefore, the secondary response takes longer to execute. This increased reaction time is known as the psychological refractory period. **A** For short SOAs (upper panel) if alcohol prolongs the perceptual stimulus detection stages this is absorbed into the bottleneck. At longer SOAs (lower panel) there is no bottleneck so prolongation of perceptual stages increases overall reaction time and this should be detected. **B** Prolongation of the central decision-making stages produces the same change in reaction time at both short and long SOAs as it has occurred after the bottleneck.

variance of the entire dataset and is not comparable to the classical ANOVAs used. An alternative approach is to assess the interaction term in a within-subjects Bayesian ANOVA (using the "BayesFactor" package in R: https://cran.r-project.org/package=BayesFactor; https://www.r-project.org). This analysis is similar to the method registered, but differs in that it incorporates the sources of variance at each level rather than summing them across conditions. This method is also more comparable to the classical statistics reported and provides a more appropriate comparison. See Supplementary Information (Section 6.2) for further detail on how the post-hoc Bayesian model comparison procedure was conducted.

Therefore, for each result we report the statistics: the pre-registered Drug x Time interaction of the classical statistical test, the pre-registered collapsed design Bayesian *t*-test, and the Drug x Time interaction for the post-hoc Bayesian ANOVA. In general, the results of the three methods are in agreement.

3. Results

Anonymised study data and guidance notes are publicly archived at https://figshare.com/s/b1640ebe17a405390ad8. Fifty-one participants were recruited, 11 of which were excluded according to the pre-registered criteria. Of the 11 exclusions, three participants had at least one session in which their inhibition function did not cross 50% failed stops and a further six were excluded for mean go-trial reaction time exceeding 600 ms (of which 4 also had inhibition functions that did not cross 50%). A further two participants withdrew after the first session. The maximum sample size of 40 was reached before any other stopping criteria were satisfied (25 female; mean age 23.5 years, SD = 3.4). Participants had a mean body weight of 68.2 kg and BMI of 23.0. As per inclusion criteria participants had AUDIT and SADQ scores below the threshold for harmful drinking (mean AUDIT = 8.1, SD = 3.0; mean SADQ = 4.1, SD = 3.2) and did not have clinical depression or anxiety (mean HADS depression scores = 2.2, SD = 2.7, anxiety scores = 5.3, SD = 2.7). Participants reached a mean peak BrAC of 48.4 μg/100 ml on average at 30 min post-drink (see supplementary material for mean breath alcohol concentration curve). Unexpectedly, males reached a higher BrAC than females by 6.4 μg/100 ml; this difference was statistically significant ($t(38) = 2.52$, $p = 0.016$, $d = 0.82$). Previous use of the alcohol administration method did not produce significant gender differences in peak BrAC (e.g., Campbell et al., 2014).

Additional checks for differences in effects between gender, block order and drink order found no significant interactions apart from a Drug x Time x Gender interaction for the dependent variable of manual SSRT (output from all analyses can be found in Supplementary Information[2]). Therefore, except for this case, we do not report further the analyses of gender, block or drink order.

3.1. Confirming alcohol intoxication

One participant failed to complete the BAES and SHAS questionnaires following alcohol administration, therefore this participant is left out of these analyses. As expected and illustrated in Fig. 3, participants were subjectively and objectively intoxicated: a 2 (Drug: Alcohol/Placebo) by 2 (Time: pre-drink/post-drink) within-subjects ANOVA of self-report measures of intoxication showed participants to be subjectively affected by alcohol as indicated by significant Drug x Time interactions for BAES and SHAS questionnaires (see Table 3 for statistical test outcomes). Participants were also objectively intoxicated as indicated by a significant Drug x Time interaction for peak saccade velocity where velocity decreased following alcohol administration (Ball et al., 1991).

3.2. Confirming manual SSRT increased during alcohol intoxication

As found in previous studies, alcohol increased manual SSRT (see Fig. 4A; Table 4 for statistical test outcomes). This effect satisfied conventional statistical significance at $p < 0.05$. The pre-registered and post-hoc Bayes factors indicated that the data were roughly twice as probable given a hypothesised alcohol effect relative to the null.

3.3. Alcohol does not increase saccadic SSRT

No significant Drug x Time interaction was observed for mean saccadic SSRTs: Fig. 4B, Table 4 for statistical test outcomes, and both the pre-registered and post-hoc Bayesian tests substantially favoured the null hypothesis.

3.4. Inconclusive evidence for greater alcohol effect on manual SSRT than saccadic SSRT

A 2 (Modality: Manual, Saccadic) x 2 (Drug: Alcohol, Placebo) x 2 (Time: Pre-, Post-Drink) within-subjects ANOVA revealed a significant Modality x Drug x Time interaction ($p < 0.05$). Both the pre-registered and post-hoc Bayesian methods yielded inconclusive Bayes factors (see Table 4 for statistical test outcomes).

3.5. Effect of alcohol on manual SSRT does not correlate with the effect of alcohol effect on saccadic SSRT

Both a Pearson's correlation and a Bayesian correlation analysis revealed no strong relationship between the difference in relative change from pre-drink to post-drink between alcohol and placebo for the saccadic task and the manual tasks ($r = 0.197$, $p = 0.22$, $BF = 0.41$), though these correlational analyses are underpowered compared to the within-subjects tests.

3.6. No clear effect of alcohol on proactive inhibition

As anticipated, proactive inhibition (defined as slower go reaction times in the stop context compared to the ignore or dual contexts) was present within both the manual task (STOP vs IGNORE $t(39) = 21.4$, $p < 0.001$, $d = 3.4$; $BF = 9.1 \times 1019$; STOP vs DUAL $t(39) = 30.7$, $p < 0.001$, $d = 4.9$; $BF = 3.9 \times 1025$) and the saccade task (STOP vs IGNORE $t(39) = 19.6$, $p < 0.001$, $d = 3.1$; $BF = 4.3 \times 1018$). The extent of this slowing can be seen in the no-signal reaction times in Fig. 5A and D).

Two-way Drug x Time interactions reveal a significant effect of alcohol on proactive slowing when comparing manual stop and ignore contexts with traditional statistics (Fig. 5B, Table 5 for statistical test outcomes), however the outcome of the pre-registered Bayesian test did not reflect this result ($BF = 0.47$). It is possible that this discrepancy is due to the baselined collapsed design used in the Bayesian analysis where variance attributable to each variable is lost when relative change measures are used. Although Figs. 5B, C and E all show similar patterns, there were no significant Drug x Time interactions for manual STOP vs DUAL contexts (Fig. 5C; Table 5) and Bayesian analyses offer no support for saccadic STOP vs IGNORE contexts (Fig. 5E; Table 5). Therefore, there is no clear effect of alcohol on proactive slowing, and even if it is present, it is clearly small (about 20 ms) compared with the overall effects of proactive slowing (100–160 ms).

3.6.1. Post-Hoc analysis: analysis of No-Signal reaction times

As the measure of proactive control was calculated from differences in no-signal reaction times, it is important to assess whether there were any alcohol induced changes to no-signal reaction time in each context. A 2 (Drug: Alcohol, Placebo) x 2 (Time: pre-, post-drink) within-subjects ANOVA was conducted on no-signal trials in the STOP and IGNORE contexts for both the manual and saccadic tasks and for the DUAL context no-signal trials in the manual task. All BFs are as the model comparison method above. As Figs. 5A and 5D suggest, alcohol significantly increased no-signal reaction times for all contexts in which

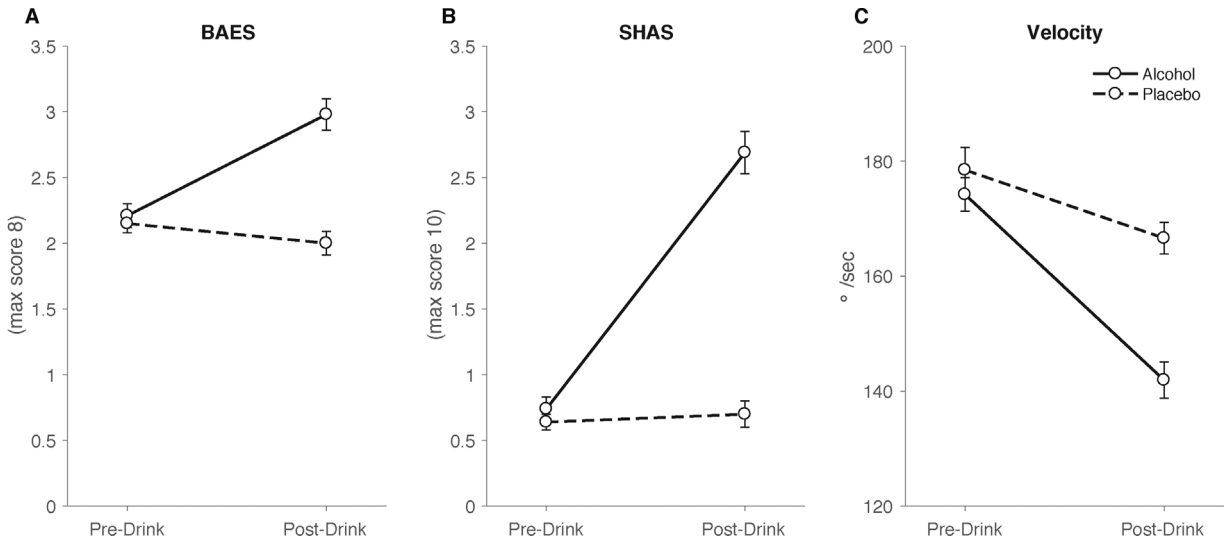

Fig. 3. Alcohol affects all mean measures of intoxication. Mean self-reported feelings of intoxication from the BAES (**A**) and SHAS (**B**) and peak saccade velocity (**C**). Error bars indicate ± 1 standard error of the mean corrected for the within-subject design (as Cousineau, 2005).

Table 3
Output of statistical analyses of intoxication conducted using pre-registered classical statistical tests, pre-registered collapsed design Bayesian *t*-tests and post-hoc model comparisons of Bayesian ANOVA Bayes factors.

Analysis	*Pre-registered*		*Post-hoc*
	Classical Drug x Time interaction	*Collapsed design Bayesian t-test*	*Model comparison Bayes Factor*
Alcohol effect on intoxication			
BAES	$F(1.38) = 15.90$, $p < .001$, $\eta_p^2 = 0.295$	BF = 37.20	BF = 43.59
SHAS	$F(1.38) = 46.25$, $p < .001$, $\eta_p^2 = 0.549$	BF = 23.31	BF = 2.36×10^9
Peak velocity	$F(1.39) = 6.88$, $p = 0.012$, $\eta_p^2 = 0.15$	BF = 126.49	BF = 4.48

Table 4
Output of statistical analyses on SSRTs conducted using classical statistical tests, collapsed design Bayesian *t*-tests and model comparisons of Bayesian ANOVA Bayes factors.

Analysis	*Pre-registered*		*Post-hoc*
	Classical Drug x Time interaction	*Collapsed design Bayesian t-test*	*Model comparison Bayes Factor*
Alcohol effect on SSRT			
Manual	$F(1.39) = 5.6$, $p = 0.02$, $\eta_p^2 = 0.13$	BF = 1.80	BF = 2.35
Saccadic	$F(1.39) = 0.08$, $p = 0.77$, $\eta_p^2 < 0.01$	BF = 0.21	BF = 0.23
Manual vs saccadic (3-way interaction)	$F(1.39) = 4.7$, $p = 0.037$, $\eta_p^2 = 0.12$	BF = 0.73	BF = 0.75

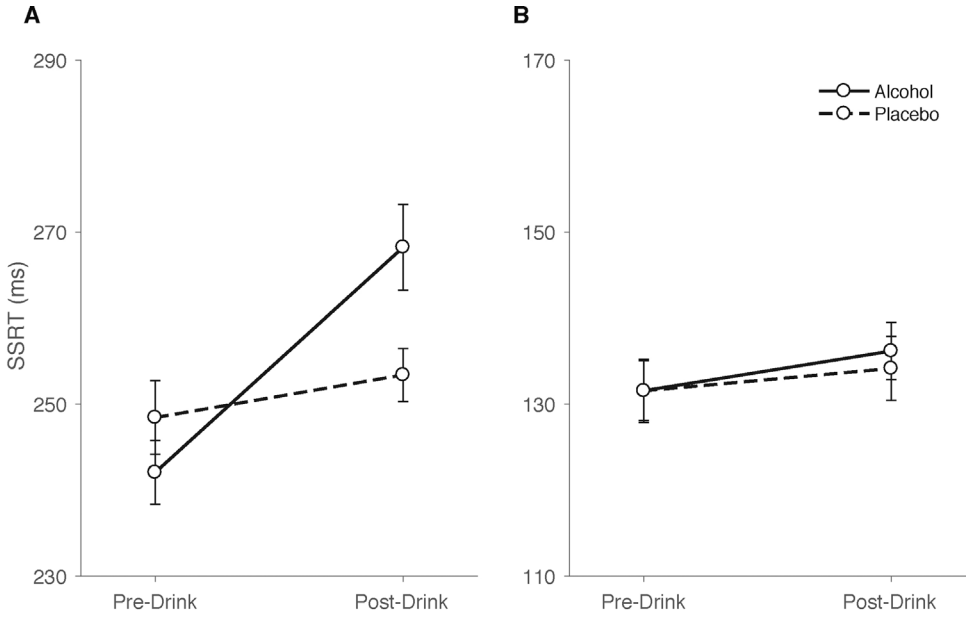

Fig. 4. Alcohol affects manual SSRT but not saccadic SSRT. Mean SSRT for: (**A**) the Manual Stop-Signal task and (**B**) the Saccade Stop-Signal task. Error bars are ± 1 standard error of the mean for within-subjects design.

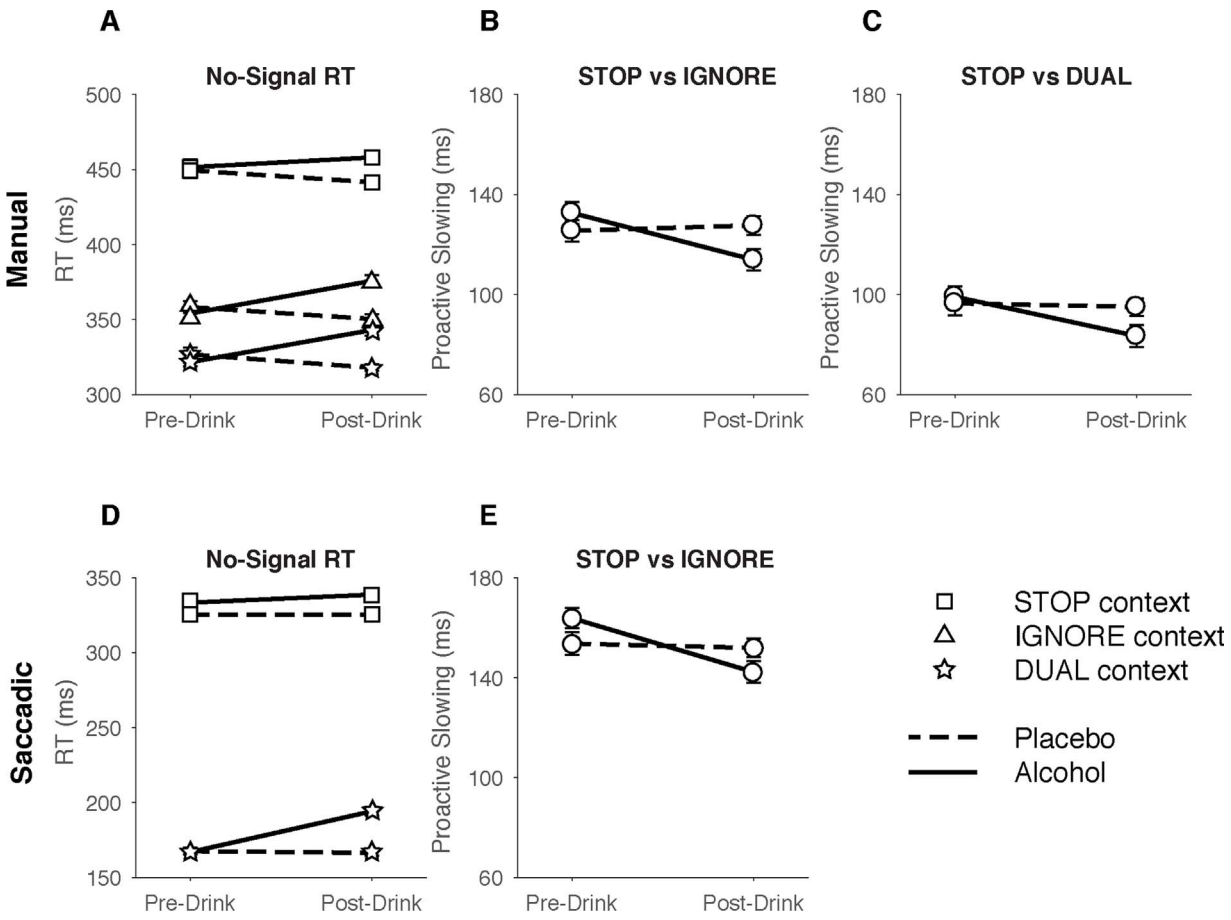

Fig. 5. There is a strong proactive slowing effect of between 100 and 160ms as demonstrated by the slower no-signal reaction times in the STOP context. The acute effect of alcohol on this slowing is small in comparison and appears to be due to motoric slowing in non-STOP contexts. A: Effects of alcohol and placebo on manual no-signal reaction times for the manual STOP context (squares), IGNORE context (triangles) and the DUAL context (stars) for alcohol (solid lines) and placebo (dashed lines); B: Effects of alcohol and placebo on proactive slowing of the STOP vs IGNORE contexts in the manual domain. Proactive slowing is calculated as the subtraction of the comparison context (e.g. IGNORE context - triangles) from the STOP context (squares). The difference between the solid lines in panel A forms the solid black line in panel B (alcohol) and the subtraction of the dashed lines forms the dashed grey line (placebo) C: Proactive slowing of the manual STOP vs DUAL contexts (squares minus stars of panel A); D: No-signal reaction times for the saccadic STOP context (squares) and IGNORE context (triangles); E: Proactive slowing of the saccadic responses (STOP vs IGNORE).

Table 5
Output of statistical analyses on proactive slowing conducted using pre-registered classical statistical tests, pre-registered collapsed design Bayesian *t*-tests and post-hoc model comparisons of Bayesian ANOVA Bayes factors.

Analysis	*Pre-registered Classical Drug x Time interaction*	*Collapsed design Bayesian t-test*	*Post-hoc Model comparison Bayes Factor*
Alcohol effect on proactive slowing			
Manual Stop vs Ignore	$F(1.39) = 5.9$, $p = 0.020$, $\eta_p^2 = 0.13$	BF = 0.47	BF = 1.93
Manual Stop vs Dual	$F(1.39) = 2.3$, $p = 0.14$, $\eta_p^2 = 0.06$	BF = 0.21	BF = 0.57
Saccadic Stop vs Ignore	$F(1.39) = 3.8$, $p = 0.06$, $\eta_p^2 = 0.09$	BF = 0.84	BF = 1.52

the participant was not required to stop their response; Manual IGNORE Drug x Time interaction: F(1,39) = 49, p < 0.001, BF = 4037; Saccade IGNORE Drug x Time interaction: F(1,39) = 41.2, p < 0.001, BF = 2.53e6; Manual DUAL Drug x Time interaction: F(1,39) = 33.6, p < 0.001, BF = 106.89. In the STOP context, there was a marginally significant Drug x Time interaction for the manual context: F(1,39) = 4.28, p = 0.045, however the Bayes factor revealed inconclusive evidence, BF = 0.65. In the saccade stop task there was no significant Drug x Time interaction F(1,39) = 0.36, p = 0.55, BF = 0.36.

These alcohol-induced increases in reaction time of no-signal trials have implications for the analysis of proactive slowing. The interpretation now, as opposed to the outcome of the pre-registered analysis alone, would be that the changes in proactive slowing occur due to the increase in no-signal reaction time in the comparison context (either IGNORE or DUAL) rather than decreases in no-signal reaction time in the STOP context that would have indicated a decrease in caution. Therefore, because the effect on the proactive inhibition measure appears to be driven by changes in the conditions that do not require response inhibition, an alcohol-induced reduction in caution cannot be concluded securely from these results.

Looking at error rates on no-signal trials in the DUAL context there was a significant Drug x Time interaction for incorrect no-signal responses where alcohol increased the number of errors (i.e., pressing left when the target appeared on the right), F(1,39) = 15.6, p < 0.001, ηp2 = 0.29; this is consistent with the increased no-signal reaction time following alcohol intoxication.

3.7. Alcohol affects action-updating

According to the logic of the PRP, set out in Sections 1 and 2.8.5 and detailed in Fig. 2, if alcohol affects any stage prior to central decision making of the secondary response (i.e., visual detection or attentional orienting toward the stimulus) then we would anticipate the difference in secondary dual response (DRT2) between post-drink alcohol and pre-

Table 6
Output of all statistical analyses conducted using pre-registered classical statistical tests, pre-registered collapsed design Bayesian *t*-tests and post-hoc model comparisons of Bayesian ANOVA Bayes factors.

Analysis	Pre-registered Classical Drug x Time interaction	Collapsed design Bayesian *t*-test	Post-hoc Model comparison Bayes Factor
Alcohol effect on action updating			
DRT2	$F(1.39) = 31.0, p < 0.001, \eta_p^2 = 0.44$	BF = 3826	BF = 201.19
Errors	$F(1.39) = 6.15, p = 0.018, \eta_p^2 = 0.14$		BF = 21.66
DRT2 by SOA	$F(5195) = 0.49, p = 0.784, \eta_p^2 = 0.012$		BF = 0.011

drink conditions and post-drink placebo to increase with the SOA. At shorter SOAs prolonged visual perception/attentional stages can be absorbed into the bottleneck period but at longer SOAs the bottleneck is much shorter or absent so this prolongation of visual perception stages increases overall DRT2. If, however, alcohol acts on the central decision-making stage or at motor execution stages of the secondary response (after the bottleneck) we would anticipate DRT2 to be uniformly elevated as a function of SOA.

Collapsed across SOA alcohol increased DRT2 as assessed by a significant 2 (Drug: Alcohol, Placebo) x 2 (Time: Pre-drink, Post-drink) interaction (see Table 6 for statistical test outcomes). To assess the effect of alcohol across SOA, a 2 (Drug: Alcohol, Placebo) by 2 (Time: Pre-Drink, Post-Drink) by 6 (SOA: 50, 100, 166.7, 233.3, 316.7, 400 ms) within-subjects ANOVA was undertaken, which revealed no significant 3-way interaction and a Bayes factor strongly in favour of the null (Table 6). These results therefore suggest that the effect of alcohol arose post-bottleneck.

3.8. Saccadic inhibition effect – additional analysis of potential interest

At the shortest SOA (50 ms) we observed dips in saccade latency distributions of signal present IGNORE trials compared to the saccade latency distributions of the no-signal distribution. These dips represent a knock-out of saccade plans, time-locked to the onset of the signal attributed to neuronal competition between saccades to the target or to the signal (e.g., Bompas and Sumner, 2011). The dips began approximately 100 ms following signal onset. The dips were not present at later SOAs as the onset was too late in the distribution. We observed no effect of alcohol on this dip; thus, no evidence that alcohol influences low-level automatic lateral inhibition within saccade execution and inhibition networks. A table of dip characteristics and a figure showing these dips can be found in the Supplementary Information.

4. Discussion

We sought to use alcohol to address the question of domain general vs domain specific response control systems. We also sought to delineate what kinds of control systems are affected by alcohol in response control tasks: reactive inhibition, proactive inhibition, action updating or attentional/perceptual systems. There were four key findings apparent from the results of this experiment. First, participants demonstrated an impairment to manual motor inhibition during alcohol intoxication, which was indexed by increased stop signal reaction time (SSRT). Second, alcohol did not show an effect on saccadic motor inhibition, where the Bayes factor indicated the data observed were 5 times more probable under the null hypothesis than the alternative. Third, there was no reliable reduction of proactive slowing during alcohol intoxication. Finally, the effect of alcohol on secondary dual responses indicates that alcohol has a more general effect than just inhibition, and its consistency across SOA indicates that alcohol influences processing following the bottleneck of the psychological refractory period; together these dual task results indicate an effect on action updating rather than perception.

4.1. Alcohol effect on manual SSRT is smaller than previously reported

Our first main result replicates a substantial literature reporting alcohol-induced impairments to manual SSRT (e.g., Caswell et al., 2013; de Wit et al., 2000; Dougherty et al., 2008; Fillmore and Vogel-Sprott, 1999; Gan et al., 2014; Loeber and Duka, 2009; McCarthy et al., 2012; Nikolaou et al., 2013; Ramaekers and Kuypers, 2006; Reynolds et al., 2006). However, the effect size and Bayes factors were smaller than anticipated. Thus, the effect of alcohol on manual SSRT may not be as robust as previously thought, possibly due previously to less powerful designs and some publication bias for positive results (see Button et al., 2013).

Of 7 previous studies (see Table 1), 4 were within-subjects designs, and of these only one used a baseline measure of inhibition (before a drink was consumed). This study (de Wit et al., 2000) had the closest design to our own, an effect size larger than ours (ηp2 = 0.26 compared to ηp2 = 0.13) but a smaller sample size (n = 17). The other studies report effect sizes ranging from ηp2 = 0.113 to 0.299 and some report larger effect sizes of Cohen's d = 0.93; however, these studies either used a between-subjects design or did not have a pre-drink or baseline condition. Given the large variability in responses to alcohol intoxication between individuals, within-subjects designs are desirable. A pre-drink or baseline measure of behaviour also provides a means for controlling for day-to-day fluctuations in behaviour. This is particularly important for the stop-signal task given its relatively low test-retest reliability in healthy individuals (Kuntsi et al., 2001; Weafer et al., 2013; Wöstmann et al., 2013; Hedge et al., 2017) i.e., intra-class correlation coefficients between 0.03 (Wöstmann et al., 2013) and 0.65 (Weafer et al., 2013).

However, despite these methodological differences, it is also possible that our measured effect size simply reflects sampling-related error around a true effect size larger than that measured here. In addition, as we have used a stopping rule to determine our sample size, based on the Bayesian outcome of our most important analysis, noise in the direction of the null may have led us to stopping at a high N, meaning that we may have underestimated our effect. If we had used a fixed N, the estimate would have been unbiased (Schönbrodt et al., 2017).

4.2. Alcohol does not affect saccadic SSRT

The lack of an effect of alcohol on saccadic inhibitory control was reflected both in classical and Bayesian statistical analyses with evidence favouring the null hypothesis five-fold over the alternative hypothesis. This is broadly consistent with some previous reports of acute effects of alcohol on saccadic inhibitory control tasks. For example, more studies report a lack of alcohol effect or even a positive alcohol effect on anti-saccade task performance (Blekher et al., 2002; Khan et al., 2003; Vassallo et al., 2002; Vorstius et al., 2008) than report an impairment (Crevits et al., 2000; Marinkovic et al., 2013). Nonetheless, studies considering the effect of alcohol on the delayed ocular response task find significant effects of alcohol on premature saccades (e.g., Abroms et al., 2006; Weafer and Fillmore, 2012). Given the correlation between hand and eye SSRT (Boucher et al., 2007) and overlap of a common functional network observed using fMRI (Leung and Cai, 2007) it was anticipated that alcohol would affect saccadic SSRT. Nevertheless, this was not the case.

It could be extrapolated that alcohol affects systems that are specific to manual responses, including manual response inhibition, whereas systems specifically related to saccadic responses, particularly the inhibition of saccades, are relatively 'immune' to alcohol intoxication.

More generally, these findings indicate that the manual and saccadic versions of the stop-signal task (as used in this experiment) are unlikely to assay the function of a single, common motor inhibition network. These findings offer support for the notion that modality specific action plans are inhibited within the neural architecture of each modality. The absence of correlation between alcohol's influence on manual and saccadic tasks was also consistent with independent effects on separate systems.

However, the 3-way interaction between Modality (manual/saccadic), Drug (alcohol/placebo) and Time (pre-drink/post-drink) offered less clear-cut support: while the traditional interaction was significant, the corresponding Bayesian analyses were inconclusive even with 40 participants. Bayesian ANOVA is yet to become mainstream and it is beyond our expertise to comment on this discrepancy. It is also possible a 3-way interaction is not the best statistical method for assessing differences in alcohol effect between the two modalities, where we expect 3 conditions to be similar (pre-alcohol and both placebo conditions) and wish to test whether one condition stands out (post alcohol), and whether this effect is different between modalities despite varying degrees of noise across all cells (Rosnow and Rosenthal, 1996).

If we accept that the simple presence of the manual effect and strong evidence against the saccadic effect points to different control systems, we can only speculate as to why these systems would be differentially sensitive to alcohol. The frontal eye fields (FEF) have been proposed as a key area involved in the inhibition of saccades (e.g., Schall and Boucher, 2007). Similarly, the pre-supplementary motor area (preSMA) has been proposed as an important area involved in the inhibition of manual responses (Cai et al., 2012; Chen et al., 2009; Nachev et al., 2007). It is possible that alcohol affects the preSMA more than the FEF, but there is no a priori reason to predict this. Rather than a difference in brain area susceptibility, we suspect the difference may be related to the unique push-pull antagonism between saccade planning and fixating known to exist within the eye-movement system (e.g., Hanes et al., 1998; Munoz and Wurtz, 1993a, 1993b). Thus, saccades can be inhibited by exciting fixation cells in a simple and fast way that is directly related to the position of the stop signal on the screen. There is no direct neuronal equivalent in manual control areas. Hand movements have a relatively longer process of execution and inhibition which may be where the system becomes vulnerable to alcohol intoxication. For saccades, the effect of alcohol on saccadic velocity indicates the system is not entirely immune to the effects of alcohol at all levels; however, it is likely the portion responsible for inhibitory control of eye movements remains functionally intact following alcohol administration at the doses used here.

4.3. Potential alcohol effects on proactive slowing could Be masked by motor slowing

It is important to distinguish proactive slowing as a measured effect in the data, and proactive slowing as a functional explanation akin to caution (there are many examples of terms with similar conflation of meaning in the literature). As a behavioural effect, it is defined as the difference in reaction time between similar types of trial in different contexts − one context where inhibition might be required and one where it never is. In this case, it is customary to use no-signal trials in the STOP context compared to either the IGNORE or DUAL context. This effect was large in all conditions (Fig. 5), but any decrease following alcohol consumption was small and inconclusive; numerically, it is only around 20 ms, in comparison to the overall proactive slowing effect of ~150 ms.

A small decrease in proactive slowing would be consistent with the trend observed in the data of Nikolaou et al. (2013) and could be explained as a decrease in caution – an impairment to functional proactive slowing − following alcohol administration. However, not only is this potential effect very small in our data, on closer inspection, the reduction in behavioural 'proactive slowing' is driven by increases in reaction time in other contexts rather than a decrease in reaction time in the STOP context. Therefore, the notion that alcohol decreases caution cannot be directly concluded by these data (Fig. 6).

4.4. Alcohol affects action-Updating and motor execution

Our results revealed a clear increase in secondary reaction time (DRT2) following alcohol as compared to post-placebo and pre-drink baseline. This result replicates previous findings reporting an effect of alcohol on dual task reaction times (Fillmore and Van Selst, 2002; Marczinski and Fillmore, 2006; Marczinski et al., 2012; Miller et al., 2009; Schweizer et al., 2005; Schweizer and Vogel-Sprott, 2008).

To establish the stage of information processing in which this effect occurs, the effect of alcohol on DRT2 across SOAs was evaluated. In the PRP logic it is assumed that the central decision-making stages cannot be conducted in parallel and thus there is a time-limiting factor for secondary responses, particularly when the temporal gap between stimuli is short (short SOAs) (Pashler, 1994). Using the locus-of-slack method, the location of an effect of alcohol on information processing can be determined as pre- or post-bottleneck. In our data alcohol increases DRT2 to a similar extent across all or most SOAs, indicating a post-bottleneck effect on decisional and execution processes. In the DUAL task participants were not required to inhibit a prepotent action plan but instead to update it to include an additional action. Thus, from our findings we conclude that this updating mechanism was impaired during intoxication, potentially also accounting for the effects on SSRT without the need for specific effects on inhibition.

However, whether alcohol has affected central decision making or motor execution stages still needs to be disentangled. Previous studies assessing effects of alcohol on secondary response times find that alcohol increased DRT2 up until SOAs of approximately 500 ms; DRT2 to stimuli that appeared after 500 ms showed no significant effect of alcohol compared to placebo or baseline (Schweizer et al., 2005). The authors argue that alcohol has affected the central decision-making stage. However, in our section on proactive slowing, we noted that the increase of no-signal reaction time in the non-stop contexts might indicate additional motoric slowing.

5. Conclusions

To summarise, the present experiment demonstrated an effect of alcohol on response control, but only when measured using manual and not saccadic responses. Alcohol also affected secondary dual responses indicating an impairment to post-perceptual action updating processes. Thus, effects of alcohol on the stop-signal task cannot be solely interpreted as impairments to inhibition. Proactive slowing − in the sense of a strategic functional inhibition akin to caution, rather than a label for a subtraction between conditions − did not appear to be affected. We conclude that alcohol impairs the execution and updating of actions in a modality-specific manner.

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Nothing declared.

Contributors

AC, PS, CC, CA and CH designed the study protocol. AC and PS managed the literature search and summaries of related work. AC, PS, CA and CC contributed to the planning of statistical analysis and power calculations. AC and CH conducted the experiment. AC analysed the data and performed statistical analyses. AC and PS wrote the manuscript and all authors reviewed the manuscript and approved the final article.

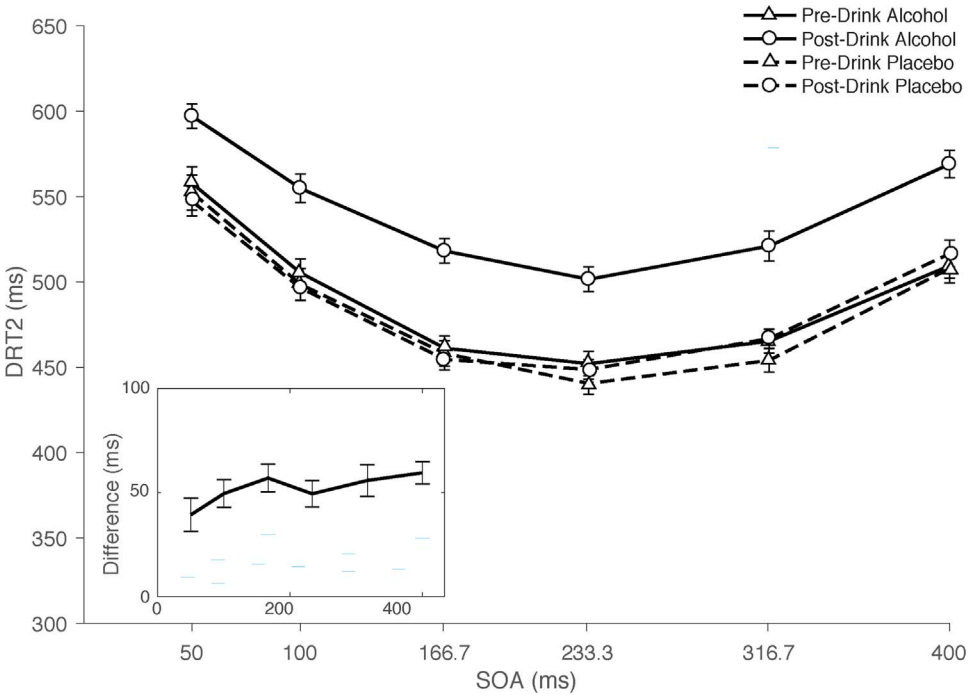

Fig. 6. Alcohol increases secondary dual response time. Mean DRT2 by SOA. Error bars are ± 1 standard error of the mean at each SOA. Inserted is the difference in DRT2 between pre- and post-drink alcohol by SOA to indicate only small fluctuations across SOA.

Conflict of interest

No conflict declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2017.08.022.

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