Real-time fMRI-based neurofeedback in depression

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Summary

Depression is one of the leading causes of disability worldwide. Currently available treatment methods are not always effective in improving depression. There is thus a pressing need for the development of novel treatment methods. Neurofeedback training can potentially alleviate symptoms of depression. By providing depressed patients with feedback about the ongoing processes in their brain via functional magnetic resonance imaging (fMRI), patients can be trained to increase the activation in positive emotion processing areas by engaging in positive imagery. The advantages of this method are that it is non-invasive, offers an individually tailored approach without any side-effects and has the capability to target the neurobiological and cognitive pathways putatively mediating depression. The main aim of this thesis was to elaborate on pilot findings that fMRI-neurofeedback has potential as an add-on treatment tool for depression (Linden et al., 2012). In doing so, this thesis does not focus on confirming that fMRI-neurofeedback can improve symptoms of depression as the dataset employed here is part of a larger dataset of a currently still running clinical trial. Instead this work investigated the feasibility of a control group receiving feedback from a scene processing area and assessed whether fMRI-neurofeedback can indeed affect emotion processing areas that function abnormally in depression and enhance perceived self-efficacy. Sixteen moderately to severely depressed patients took part in a course of five neurofeedback training sessions in which all patients learned to up-regulate the activation in their individually localised target areas. The patients that had received feedback from a positive emotion area influenced the activity in a wider emotion regulation network than just their target area. Additionally, the acquisition of self-regulation skills significantly improved scores on a self-efficacy scale. These findings confirmed the ability of neurofeedback to target biological and cognitive pathways putatively mediating depression.

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Contents

Chapter 1 - Depression

Mental illness constitutes a major threat to global public health. One of the most prevalent mental disorders is major depressive disorder (MDD). Not only does this debilitating disorder have a detrimental impact on the overall well-being of patients and their caregivers, the economic burden is also enormous as depression can lead to productivity loss, disability and unemployment (Wang, Simon, & Kessler, 2003). An epidemiological study carried out in the United States found that depressed patients were unable to carry out their daily activities such as work and household tasks at, on average, 35 days out of a year due to their illness (Kessler et al., 2003). More than 120 million people world-wide are estimated to suffer from this disorder and calculations from the World Health Organisation suggest that by 2020 depression will be the second largest cause of disability (Murray & Lopez, 1997). One reason for the high prevalence of depression is that 30% of patients do not benefit from currently existing treatment options such as anti-depressant medication (Rush et al., 2006). Moreover, the likelihood of developing another depressive episode increases dramatically as a function of the number of previously experienced episodes (Burcusa & Iacono, 2007; Lewinsohn, Zeiss, & Duncan, 1989), ranging from 60% after a single episode to 90% after three episodes (Winans & Bettinger, 2004).

The main aim of this thesis was to elaborate on the findings of a pilot study that showed that functional magnetic resonance imaging (fMRI)-based neurofeedback training has potential as an add-on treatment method for depression (Linden et al., 2012). This thesis investigated whether a neurofeedback intervention in a group of depressed patients affected pathways putatively involved in the instigation and continuation of depressive symptoms. As the data collected for this thesis forms part of larger dataset of a currently still ongoing clinical trial, this thesis does not examine whether neurofeedback training results in a clinical improvement of depression. The current chapter provides an introduction to the pathophysiology of depression. Chapter 2 gives an overview of neurofeedback training based on fMRI. Chapter 3 sets out the

rationale behind the chosen intervention to alleviate symptoms of depression. In order to identify the most suitable control group design for this clinical intervention, Chapter 4 investigates the perceptual changes that neurofeedback of higher visual processing areas can induce. It will also provide more insight into the brain-behaviour relation of higher visual areas. Chapter 5 describes the feasibility of neurofeedback to target the neurobiological substrate of depression based on the physiological self-regulation performance of the patients taking part in the intervention study. Chapter 6 describes the changes in brain activation at the whole-brain level that are associated with the intervention. The indirect effect that neurofeedback can have on maladaptive cognitive processes in depression via influencing self-efficacy is discussed in Chapter 7. Chapter 8 investigates whether a potential improvement in the proposed neurofeedback training could be obtained via the use of pattern-based, opposed to region-specific, feedback. Finally, Chapter 9 presents a summary, interpretation and integration of the findings set out in this thesis.

1.1 Symptomatology

Depression is mainly characterised by a lack of enjoyment of previously pleasurable activities, a symptom known as anhedonia (Snaith, 1993), and by low mood, defined as feelings of sadness, helplessness, guilt and worthlessness. To be diagnosed with depression according to the criteria of DSM-IV-TR (APA, 2000), one of these symptoms must be present for at least two weeks. In addition, the patient must display another four symptoms at the same time which could be any of the following: feelings of guilt or worthlessness, concentration problems or indecisiveness, disturbances in sleeping pattern, low energy levels or fatigue, psychomotor retardation or agitation, thoughts of death or suicidal ideas, significant changes in weight or changes in appetite. Although the DSM-IV-TR offers guidelines to diagnose depression, these are not always clear-cut and leave room for interpretation differences. In addition, high comorbidity rates have been found between mood disorders, post-traumatic stress disorder (PTSD) and generalised anxiety disorder but depression can also

be co-morbid with substance use disorders, panic disorder (with agoraphobia) and social phobia (Brown, Campbell, Lehman, Grisham, & Mancill, 2001). Additional diagnostic challenges arise if a patient is unwilling or unmotivated to cooperate, or is struggling to do so because of indecisiveness. In response to these uncertainties of traditional clinical diagnosis, the number of studies investigating diagnostic biomarkers of depression has surged over the last years. However, this has not resulted in the identification of any biomarkers that can be utilised for the reliable diagnosis of depression (Schmidt, Shelton, & Duman, 2011). One reason for this is that markers of depression may not be constant or express themselves differently depending on environmental factors (Linden, 2013). So whether biomarkers will result in an adequate solution to the diagnostic issues associated with depression can be questioned.

1.2 Etiology

Depression is an etiologically hetereogenous disease (Winokur, 1997). The numerous putative causal factors associated with depression can be grouped in several different types. In this thesis, these factors have been categorised as cognitive-behavioural factors, biological factors and environmental factors. The boundaries of each category are not absolute as aspects of these categories overlap. The intricate interactions will therefore be discussed in section 1.2.4 that links these factors together. Please note that a causal relation can be established relatively conclusively for some of these factors, such as adverse life events, but for most there is no consensus as to whether each association is one of cause or effect.

1.2.1 Cognitive-behavioural factors

Various psychological models of depression have been proposed over time (see for instance (Dalgleish, 2004) for a review). As the rationale for a neurofeedback intervention in depression is based on Albert Bandura's self-efficacy theory, this chapter will only review this account which explains the causal factors of depression in terms of perceived self-efficacy. Self-efficacy

theory predicts that motivation, i.e. how willing someone is to initiate certain behaviours, with how much effort and for what duration, is depending on expectations regarding the likelihood of achieving the desired outcome. These expectations depend first of all on a person's outcome expectancy, which is an estimate of how likely a certain behaviour will result in a particular outcome. How much control one deems to have over external events is one instance that influences outcome expectancy. Secondly, these expectations depend on efficacy expectancy, which is the perceived likelihood of being able to execute this behaviour given someone's performance history, vicarious experience, verbal persuasion and physiological state (Bandura, 1977). The self-efficacy model predicts that high self-efficacy beliefs can enhance performance (Bandura, 1989). Several studies investigated this link between perceived self-efficacy and performance. Barling & Beattie (1983) found a positive correlation between self-efficacy and sales performance as measured by number and revenue of insurance policy sales and number of sales calls. Other studies tested for a relation between self-efficacy scores and academic performance and confirmed a similar relationship (Lent, Brown, & Larkin, 1984; Wood & Locke, 1987). However, an important limitation of most of these studies is that they do not take the competence of their subjects into account. The problem applies to the study by Lent et al. (1984) who studied the relation between perceived self-efficacy and academic performance. After all, it is conceivable that self-efficacy expectations reflect (rather than cause) someone's actual academic capability. Similarly, Rychtarik, Prue, Rapp and King (1992) compared self-efficacy with the relapse rate in individuals receiving treatment for alcohol dependence. Individuals who scored lower on self-efficacy ratings at intake were more likely to have had a relapse at follow-up. In addition, of all relapsed individuals, those with lower self-efficacy scores consumed more alcohol at follow-up. However, individuals who rated their self-efficacy as higher may actually have been in circumstances which promoted abstinence while those with lower self-efficacy scores may have found themselves in unfavourable circumstances. These circumstances may include for instance someone's support network (Havassy, Hall, & Wasserman, 1991) and financial situation (Siahpush & Carlin, 2006). It could thus have been the case that self-efficacy did not reflect the subjective confidence in being able to remain abstinent but instead reflected a relatively

more objective measure of how likely someone was to succeed given the circumstances.

One of the strengths of self-efficacy theory is that it can explain why individuals with equal skills do not necessarily end up with equal performance levels and can thus account for differences between an individual's competence and performance. This implies that in order to test this theory appropriately, either self-efficacy scores need to be manipulated experimentally within an individual or between groups with comparable competence (Cervone & Peake, 1986). Alternatively, groups with comparable self-efficacy scores but differing competence levels need to be compared. In response to this need Bouffard-Bouchard (1990) performed a study in which perceived self-efficacy was experimentally manipulated while participants were given an unfamiliar verbal concept-formation task. After a set of three initial problems, participants either received positive or negative feedback as to how they had performed in comparison with their peers. Participants were then given another four concept-formation problems to solve. The competence level, as defined by how many of the initial problems were solved, which cognitive strategies were employed during the final four problems and the number of required attempts before the right answer was reached, did not differ between the high and low self-efficacy group. Nevertheless, the high self-efficacy group had completed significantly more problems and used more efficient problem-solving strategies. Sanderson, Rapee, & Barlow (1989) explored the tenets of self-efficacy in a more systematic way by investigating the relation between self-efficacy and panic attacks in patients with agoraphobia while manipulating self-efficacy. The exact same level of carbon dioxide was administered to both groups, yet one group was led to believe that they could exercise some control over the carbon dioxide intake by closing a valve. The other group was informed of not having any control over this intake. As predicted by self-efficacy theory, the latter group experienced a higher number of panic attacks compared to the former group. Along with the finding that it does not seem to be the frequency of intrusive thoughts that determines anxiety arousal but rather the perceived control one has over these thoughts (Kent & Gibbons, 1987; Kent, 1987), these studies offer compelling evidence for the self-efficacy theory. Nevertheless,

some evidence has also been published against Bandura's self-efficacy theory. Vancouver & Kendall (2006) for instance found that when students had higher self-efficacy beliefs, they studied less for their exams than when those beliefs were lower. Bandura & Locke (2003) identified several conditions in which negative efficacy effects could occur. They, for instance, stressed the difference between preparatory and performance aspects of functioning, with self-doubt during preparatory stages providing a potential incentive to acquire certain knowledge and skills. At the same time, they underlined the importance of perceived *learning* self-efficacy during preparatory phases of goal achievement. Another argument against self-efficacy theory arose from the finding that the relation between global self-efficacy measures and academic performance was not always consistent. In reply, Bandura stressed the task and situational specificity of self-efficacy and the importance of task and context specific assessment opposed to more global measures of self-efficacy (Zimmerman, 1995).

Bandura suggested that depression is mediated by inefficacy with regard to 1) performance monitoring and achieving aspirations, 2) thought control and 3) social skills. The first two factors are partly intertwined. Maladaptive performance monitoring processes include attributing successes to external factors while attributing failures to personal deficiencies, distorting recollections of successes in self-dejecting ways and comparing accomplishments against other persons who may have a completely different set of capabilities and goals (Schwartz, 1974). These processes can all lead to self-devaluation, especially since depressed patients have been found to set themselves unrealistically high goals (Bandura, 1997). At the same time depressed patients have been found to dwell on failures rather than to reminisce over successes. This is closely related to inefficacious thought control, one of the most important factors in depression, as depressed patients tend to eliminate positive thoughts and ruminate over negative thoughts. Perceived inefficacy to control unwanted thoughts can be experienced as very debilitating and its importance is highlighted by the finding that the greater the thought control efficacy induced by a treatment, the greater the improvement from depression and the smaller the likelihood of relapse (Bandura, 1992). It must be noted that

thought control in this context refers to the ability to regulate one's own thought and not to the feeling that an external entity is controlling one's thoughts as patients suffering from schizophrenia may experience.

Beck's cognitive model of depression (Beck, 1967) can account for how the focus on negative information arises. Beck proposed that these processes are likely to occur because of negative self-schemata, which are internally stored representations of ideas and experiences related to the self. These act as a filter for schema-congruent information from the environment thereby biasing attentional, interpretive and memory processes towards the negative aspects that are encountered. In addition they can cause neutral events to be interpreted in a negative light. This results in the verification and crystallisation of negative self-schemata leading to a pessimistic outlook on the self, world and future, which is the purport of Beck's influential cognitive triad (Beck, Rush, Shaw, & Emery, 1987). (The formation of negative self-schemata will be discussed in section 1.2.4) Attentional biases towards negative cognitions can then lead to ruminations, for instance about one's failures. Interpretive biases can cause problematic emotional and self-referential processing, which for example occurs when ambiguous information is interpreted in a negative light. Memory biases for instance result in the selective encoding of negative information. Research has even found biases in automatic sensory processing. Sterzer, Hilgenfeldt, Freudenberg, Bermpohl and Adli (2011) used a continuous flash suppression paradigm in which either a fearful, happy, sad or neutral emotional face was presented to one eye while high-contrast dynamic patterns were flashed to the other eye. Depressed patients were faster than healthy control in identifying the location of sad faces, but slower in locating happy faces. Together these biases perpetuate negative ideas about the self (and others) thereby maintaining the depressive episode.

A large body of evidence supports the tenets of Beck's model. Especially self-negativity, mood-congruent recall and specificity to focus on loss have been supported by research into depression (Haaga, Dyck, & Ernst, 1991). Joormann and Gotlib (2010) found that patients suffering from depression experience difficulties especially with inhibiting negative information and that attentional

biases to negative aspects occurred particularly when the presented information involved the self. Also biases in memory processes have been found in depressed patients that resulted in a focus on the miserable aspects of their lives (Teasdale, 1983) and on negative material (Matt, Vazquez, & Campbell, 1992). What is more, any bias to selectively attend to sad faces as opposed to happy or neutral faces, as found in melancholic depression, seem to outlast the depressive episode. This may increase the vulnerability to future depressive episodes (Joormann & Gotlib, 2007; Linden, Jackson, Subramanian, Healy, & Linden, 2011).

In addition to inadequate performance monitoring and thought control, inefficacious social skills can contribute to depression by creating an environment providing little support (see also section 1.3.3). Although inefficacy beliefs with regard to performance monitoring, thought control and social skills each have their own characteristics, they are interwoven with each other. For example, rumination in itself can also decrease social support levels (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008) and enhanced attention to negative stimuli can affect the encoding and thus accessibility of negative memories.

1.2.2 Biological factors

Due to the resemblance between symptoms of depression and sickness behaviour induced by pro-inflammatory cytokines, cells of the immune system, it has been suggested that inflammation can trigger depression (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). In support of this, higher prevalence rates of depression have been found in individuals suffering from a chronic medical illness (Dohrenwend & Dohrenwend, 1974), although secondary effects of physical illness on mood may also contribute to such findings. Other biological factors associated with depression are discussed below.

Genetic risk factors

Epidemiologic studies have found the heritability of depression to be approximately 45% (Belmaker & Agam, 2008; Nestler et al., 2002). Other studies found that the likelihood of developing depression is 1.5-3 times higher in individuals with a first-degree relative who has had a depressive episode (Winans & Bettinger, 2004). The actual genes underlying these findings are still under investigation.

Neurobiology of emotion and depression

Depression has also been associated with abnormal physiological processes in the brain. Chapter 3 relates these physiological deficits to neurofeedback implementations, which currently targets brain abnormalities at the macroscopic level. The current section therefore focuses on potential macroscopic abnormalities.

A wide range of studies has been dedicated to identifying the structural and functional abnormalities underlying depression. This research has been complicated by anti-depressant medication targeting brain functioning. Any identified changes in brain activity could namely be related to the depression itself, but could also be a consequence of medication intake. This may explain why findings have often shown discordance, which in addition may be due to differences in sample characteristics such as age at depression onset and exact symptomatology. Nonetheless most studies seem to agree that both classical limbic and higher-order cognitive control areas play a key role in depression. While metabolism and blood flow is increased in paralimbic cortical and subcortical structures during depressive episodes, reductions in both have been exhibited in more dorsally located cognitive control areas (Phillips, Drevets, Rauch, & Lane, 2003b). The limbic system as described by Broca, Papez and MacLean (MacLean, 1955) encompasses a wide range of areas such as the hypothalamus, thalamus, hippocampus and the cingulate cortex. An extensive array of both afferent and efferent connections, partly mediated via the mamillothalamic tract, thalamocortical projections and fornix, maintain an equilibrium that is potentially vital to healthy emotion processing. In

depression, areas involved in emotion modulation and inhibition such as the dorsolateral prefrontal cortex (DLPFC; Mayberg et al., 1999) and anterior cingulate cortex (ACC; Drevets et al., 1997) have shown reductions in metabolism and blood flow, while areas related to emotion perception and production, such as the ventral striatum, anterior insula, amygdala and thalamus, have shown elevated resting cerebral blood flow and glucose metabolism (Drevets, 2000, 2001; Lorenzetti, Allen, Fornito, & Yücel, 2009; Phillips, Drevets, Rauch, & Lane, 2003b). The balance between top-down emotion control and bottom-up emotion generation processes thus seems vital for our (emotional) well-being (Mayberg, 1997). The main areas related to emotion processing and depression will be discussed next and are summarised in Table 1.1. This table does by no means provide a full account of all brain abnormalities associated with depression, but presents a global overview of regions involved.

PREFRONTAL AND CINGULATE CORTEX

The prefrontal cortex seems essential for the achievement of goals and it has been suggested that the left and right hemisphere function slightly differently to fulfil this purpose. The left prefrontal cortex has been related to approaching desired goals, while the right side seems to be involved in the inhibition or withdrawal from certain behaviours. It has been suggested that shifts in the activation ratio between left and right frontal regions occur in depression. While the relative activation of frontal regions on the left compared to the right seems reduced, the relative activation of the right seems increased (Paquette, Beauregard, & Beaulieu-Prévost, 2009; Thibodeau, Jorgensen, & Kim, 2006; Tomarkenand & Keener, 1998). Hyperactivity in the right DLPFC has even been found to correlate with depression severity (Grimm, Beck, et al., 2008; Osuch et al., 2000). These findings might be related to symptoms of depression such as the lack of engaging in enjoyable activities. One of the brain areas playing a prominent role in executive control is the DLPFC. This region, along with the dorsomedial prefrontal cortex (DMPFC), has been found to be involved in conflict monitoring (Mitchell et al., 2009) and is of importance in emotion regulation (Ochsner & Gross, 2005). Evidence for the abnormal activity displayed in this brain region in depression is abundant (Baxter,

Schwartz, Phelps, & Mazziotta, 1989; Bench, Friston, Brown, Frackowiak, & Dolan, 2009; Harvey et al., 2005; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007). It has been suggested that this abnormality reflects the non-specific slowing of cognitive processing (Drevets, 1998) and reduced top-down control of subcortical affective circuitry (Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007). Decreased activity was for example found during resting state (Baxter et al., 1989), but also when depressed patients were asked to perform a digit sorting task, a task known to require executive control and known to selectively recruit the DLPFC in healthy subjects (Siegle et al., 2007). Interestingly, reduced DLPFC activity did not result in impaired task performance. Another study that used the *n*-back task found that depressed patients showed more extensive involvement of the DLPFC to reach a similar performance level as healthy subjects (Harvey et al., 2005). While the involvement of the DLPFC in emotion processing is mainly on the regulatory front, the ventrolateral prefrontal cortex (VLPFC) appears to play a role in the regulation as well as in the production of affect. VLPFC involvement has for example been found during a cognitive reappraisal task involving aversive images (Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). Furthermore, the establishment and extinction of valence-stimulus contingencies are also (partly) reliant on the VLPFC (Morris & Dolan, 2004; Rolls, 1996). Inconsistent findings have been reported with regard to VLPFC activity in depression, yet most studies seem to report increased activation assumed to be related to ongoing emotional processing (Davidson et al., 2002; Drevets, 1998). The ventromedial prefrontal cortex (VMPFC) has also been implicated in depression and includes the orbitofrontal cortex (OFC) and subgenual anterior cingulate, the latter of which will be discussed in more detail below. The OFC has been implicated in reward-processing and habit formation as it has been found to code for outcome associations with different stimuli and actions (O'Doherty, 2007). Distinct roles for the left and right OFC have also been proposed. The left OFC seems particularly responsive to rewards and the right to punishments (Davidson et al., 2002). In depression, reduced volume and decreased glucose metabolism have been found in the OFC (Bremner et al., 2002; Davidson et al., 2002). Moreover, an inverse correlation has been found

between depression severity and activation in the posterior lateral and medial OFC (Drevets, 2007).

The main function of the ACC appears to be two-fold, with a central role in cognitive processes which is subserved by its dorsal part and a role in affect mediated by the rostal and ventral subdivisions (Davidson et al., 2002). The cognitive part of the ACC is mainly involved in conflict monitoring and attention. Its connection with the DLPFC suggests it signals the DLPFC when cognitive control is required. This could explain how reduced gray and white matter and hypoactivity in this area in depression can result in impaired cognitive control, as well as how the attentional deficits come about (van Tol et al., 2010). The affective subdivision of the ACC on the other hand has been found activated during different emotional states and during behaviours requiring monitoring processes. It is therefore suggested to be involved in social behaviour, emotional expression and in regulating visceral and autonomic responses to emotional events. Hypoactivation in this region during depression could explain the inability to experience certain emotions and the hypersensitivity to failure or guilt (Drevets, Price, & Furey, 2008). Osuch et al. (2000) found a correlation between depression severity and regional cerebral metabolism in the right anterior cingulate after controlling for anxiety scores, age and gender, although it must be noted that this was in a sample containing both unipolar and bipolar patients. The roles of the subgenual and perigenual ACC in depression have been extensively studied. The subgenual anterior cingulate cortex (sgACC) is activated during for instance experimentally induced sadness, but also during the evaluation of the emotional valence of (un)pleasant words (Drevets et al., 2008). Lesions that include the sgACC result in dysfunctional emotional behaviour such as the inability to take cues containing information about punishment and reward into account. As such, the role of the sgACC seems to be the autonomic regulation of emotional behaviour (Critchley, 2005; Davidson et al., 2002). Activation levels in this area seem to be elevated in depression and correlate with depression severity (Drevets et al., 2008). As for the perigenual anterior cingulate cortex (pgACC), Mayberg et al. (1997) found that the metabolism before anti-depressant medication treatment differentiated responders from non-responders. Those with an initially elevated

metabolism were more likely to benefit from the treatment than those with reduced metabolism, compared with healthy controls. The number of depressive episodes and the duration of the current episode could not account for the differences in metabolism found. Once remitted, experimentally induced sadness led to reduced pgACC metabolism while currently depressed patients did not show this effect (Greicius et al., 2007). In healthy emotion processing, this area is consistently activated in response to anxiety and sadness.

AMYGDALA

The amygdala seems to be one of the key areas in depression. It has been widely established that the amygdala is involved in (conditioned) fear processing (LeDoux, 2003). Yet, the amygdala does also play a key role in the detection of other emotions (Costafreda, Khanna, Mourao-Miranda, & Fu, 2009). Lesion studies have for instance shown that the amygdala plays a crucial role in processing social signals, for example facial expressions (Dalgleish, 2004). Additionally, the amygdala is involved in the encoding and retrieval of emotionally loaded memories (Siegle et al., 2007). Related to this the activation in the amygdala in depression has been found to be greater during the implicit processing of sad faces (Suslow et al., 2010; Victor, Furey, Fromm, Ohman, & Drevets, 2010) and sustained to negative words (Siegle, Ingram, & Matt, 2002; Siegle et al., 2007). In contrast, reduced activation levels were measured after the implicit processing of happy faces (Suslow et al., 2010; Victor et al., 2010). In addition to these functional abnormalities, a reduction has been found in the number of glial cells in the amygdala of depressed patients (Bowley, Drevets, Dost, & Price, 2002). Both increased and decreased amygdalar volume has been reported in depression. Chronic or intermittent depression is mainly associated with volume reductions (Drevets et al., 2008). Moreover, an elevated glucose metabolism and resting cerebral blood flow (CBF) have been reported (Drevets, 2003). Furthermore, a positive correlation has been reported between the metabolism in the amygdala and depression severity (Abercrombie et al., 1998; Drevets, 2001).

STRIATUM

The dopamine-rich innervations of the striatum, especially of the nucleus accumbens, have linked this structure to reward processing. The dorsal striatum includes most of the caudate and putamen and seems to play a prominent role in reward learning and reward-obtaining behaviour. The ventral striatum, which is comprised of the nucleus accumbens and the ventral part of the caudate and putamen, on the other hand seems to be more involved in reward anticipation (Knutson, Fong, Adams, Varner, & Hommer, 2001). The striatum also seems to play a role in aversive processing (O'Doherty, 2004). The activation in the ventral striatum does not only show deviations in depression during rest (see section 1.2.2), but also during reward processing. While the presentation of positive affective stimuli normally induces an increase in ventral striatum activity, a reduced blood oxygenation level dependent (BOLD) response has been found in depressed patients relative to controls in response to monetary rewards (Pizzagalli et al., 2010) and positive words (Epstein et al., 2006). The former study additionally found a negative correlation between caudate volume and anhedonic symptoms. Anatomical changes were also found in the ventral part of the striatum, where decreased gray matter has been reported as well (Husain et al., 1991; Krishnan et al., 1992).

INSULA

The initially established function of the insula was mainly an involvement in the processing of disgust (Murphy, Nimmo-Smith, & Lawrence, 2003), yet its function appears to be much broader than that. The insula has reciprocal connections with a wide range of areas, such as the central nucleus of the amygdala and viscerosensory systems. The latter results in the insula playing a role in visceral sensory and motor phenomena, such as taste and cardiovascular functioning (Augustine, 1996). In addition, the insula becomes activated during the emotion induction by emotional recall or imagery (Phan, Wager, Taylor, & Liberzon, 2002). Hypoactivation of the posterior insula has been found in depressed compared to healthy individuals at rest (Fitzgerald, Laird, Maller, & Daskalakis, 2008) and during the viewing of positive and negative images (Lee et al., 2007). Moreover, this decreased responsiveness to negative images in the left insula was correlated with depression severity. The anterior insula on the

other hand has shown increased CBF and metabolism, as well as reductions in volume (Drevets, 2000; Takahashi et al., 2010). Another study measured regional homogeneity to investigate the temporal synchrony in the activation of neighbouring voxels during resting state (Liu et al., 2010). Depressed patients, as well as those with a genetic risk for developing depression, showed decreased regional homogeneity in the insula compared to healthy controls.

THALAMUS

The thalamus is the relay station of the brain, playing an important part in signalling information from for instance subcortical structures to the cingulate gyrus. Abnormally high blood flow and metabolism has been found in the medial thalamus of acutely depressed patients (Drevets, 2000), which has been found to be decreased in the remitted state (Holthoff et al., 2004). Increased metabolism has been found to be reinstated after the induction of depressive symptoms by tryptophan depletion (Neumeister et al., 2004).

HYPOTHALAMUS

Located deep within the brain, the hypothalamus plays a vital role in controlling basal functions such as eating, sleeping and sexual drive (Jansson, Hellsten, & Tingström, 2006). Changes in many of these functions are prominent in depression, which are known as the neurovegetative symptoms of depression and thus suggest abnormal hypothalamic function in depression (Nestler et al., 2002). The implication of the hypothalamus in depression has mainly been investigated in the context of the hypothalamus-pituitary-adrenal (HPA) axis. The hypothalamus influences the pituitary via the secretion of corticotrophin-releasing factor, which results in an increased synthesis and release of adrenocorticotrophin (ACTH). This in turn influences the adrenal cortex, which will increases the production and secretion of glucocorticoids, which are known to have a profound effect on metabolism and behaviour. Approximately 50% of patients suffering from depression show heightened HPA axis activation (Nestler et al., 2002).

HIPPOCAMPUS

Depression has been related to impairments in specific aspects of memory, which may be related to the hippocampus (Burt, Zembar, & Niederehe, 1995). For instance, depressed patients showed reduced hippocampal activation during the recall of autobiographical memories (Young et al., 2012). Abnormal functioning of the hippocampus potentially arises due to the indirect effects of stress. Stress increases glucocorticoid levels, which can have a detrimental effect on hippocampal neurons. In concordance, elevated levels of cortisol have been found in approximately 45% of MDD patients (Bremner et al., 2000). Furthermore a negative correlation between depression duration and hippocampal volume has been reported (Sheline, Gado, & Kraemer, 2003).

The wide range of functional abnormalities identified in depression is generally concomitant with structural abnormalities. The atypical activity levels found in the pgACC and OFC occur alongside reductions in volume and glial cell density (Drevets et al., 1997). Studies into the sgACC found a reduction in volume by 48% and in glial cell number by 24% in a sample of depressed patients with a family history of mood disorders (Davidson et al., 2002). Other parts of the frontal cortex show structural changes as well. Both the VLPFC and DLPFC have shown reduced neuronal cell density. In addition, the volume of the caudate, nucleus accumbens and hippocampus is abnormally reduced in depression (Bremner et al., 2000). These reductions in structure do not necessarily entail reductions in activity as reduced glial cell density has also been reported in the amygdala, which generally shows elevated activity in depression. Also, what initially seemed reduced activation in the sgACC appeared to be elevated activity levels when volumetric reductions were taken into account (Drevets, 2000). Findings from studies investigating neural changes induced by successful anti-depressant treatment correspond to the findings of functional studies as well, showing a decrease in neocortical areas and an increase in limbic-paralimbic areas before treatment. Mayberg et al. (1999) investigated the neural changes accompanying a decrease on the Hamilton Depression Rating Scale (HDRS) by 50% or more after a six week treatment with paroxetine or a placebo. Increases in glucose metabolism had occurred in the DLPFC, dorsal anterior cingulate and posterior cingulate, while

metabolism had decreased in the sgACC and insula. Analogue decrements in the blood flow in the sgACC have been found after electroconvulsive therapy (ECT) and deep brain stimulation (DBS; Nobler et al., 2001). Kennedy et al. (2001) also found increased glucose metabolism in several prefrontal regions, alongside decreases in the hippocampal and parahippocampal regions after a reduction in depression severity induced by paroxetine treatment. Yet another study found that elevated activation levels in the amygdala returned to normal after successful anti-depressant medication treatment (Drevets, 1999). Experimentally induced relapse, with for instance tryptophan depletion, was concomitant with increased sgACC metabolism (Drevets et al., 2008). On the other hand, abnormal activation in the OFC has not consistently been reported to normalise after successful treatment, but decreases in activation in the VLPFC seem to occur after a range of treatments including paroxetine, venlafaxine and ECT (Brody et al., 1999; Kennedy et al., 2001). Activation in the bilateral putamen was found to be significantly decreased upon remission (Holthoff et al., 2004).

Area	Anatomical abnormalities	Activation abnormalities
Prefrontal cortex	**Dorsolateral** • Reduced gray matter **Ventrolateral** • Reduced gray matter volume **OFC** • Reduced volume	**Dorsolateral** • Decreased BOLD response during resting state and executive control (left) **Ventrolateral** • Increased CBF and metabolism (left) **OFC** • Decreased glucose metabolism
Cingulate	**Dorsal ACC** • Reduced gray and white matter (left) **Rostral/ventral ACC** • Reduction in gray matter	**Dorsal ACC** • Reduced metabolic activation **Rostral/ventral ACC** • Increased CBF and metabolism when accounted for volume reductions (left) **Posterior** • Increased metabolism
Amygdala	• Both increased and decreased volume reported. Chronic or intermittent depression is mainly associated with the latter.	• Sustained activity during processing negative emotional information (left) • Increased CBF and metabolism

Table 1.1. Overview of brain areas showing abnormalities in depression. BOLD = blood oxygenation level dependent, CBF = cerebral blood flow, OFC = orbitofrontal cortex, ACC = anterior cingulate cortex.

Area	Anatomical abnormalities	Activation abnormalities
Striatum	**Dorsal** • Decreased volume **Ventral** • Decreased volume	**Dorsal** • Decreased CBF and metabolism **Ventral** • Increased blood flow
Insula	**Anterior** • Reduced volume (left)	**Anterior** • Increased CBF and metabolism **Posterior** • Reduced metabolism (left)
Thalamus	• None reported	**Medial** • Increased CBF and metabolism (left)
Hippocampus	• Negative correlation volume and depression duration	• Reduced activity during generating specific autobiographical memories (left)

Table 1.1. Continued.

Given the extensive interconnectivity in the brain, anatomically specific abnormalities in depression should not be evaluated in isolation. It is important to bear in mind that increases in blood flow or metabolism can either result in excitation or inhibition depending on the type of projection. The previously described HPA axis seems under control of the hippocampus and amygdala (Nestler et al., 2002). Excitatory connections link the amygdala and several regions of the prefrontal cortex with each other and the mediodorsal nucleus of the thalamus (Drevets, 1999). The sgACC also shares connections with the amygdala, the mediodorsal as well as periventricular nucleus of the thalamus and the striatum (Drevets et al., 2008). Within the prefrontal cortex, the VLPFC and OFC have the most widespread connections with subcortical emotion processing areas. Several studies have found imbalances in limbic-thalamo-cortical circuits, involving the amygdala, medial thalamus and ventral prefrontal cortex, as well as limbic-striatal-pallidal-thalamic and prefrontal-amygdalar-pallidostriatal-mediothalamic circuits in depression (Anand et al., 2005; Drevets, 2001). To measure the connectivity between areas forming parts of mood regulation circuits Anand et al. (2005) measured the correlations of low frequency blood oxygenation level-dependent fluctuations (LFBF) in response to positive, negative and neutral pictures. At baseline, significant connectivity differences were found between depressed patients and matched controls during rest and during the presentation of both positive and negative pictures. These differences were mediated by reduced connectivity between the ACC on the one hand and the medial thalamus and pallidostriatum on the other hand in depression. After six weeks of sertraline treatment the connectivity between the medial thalamus and dorsal ACC normalised during rest and positive picture presentation, but not for negative picture presentation.

Apart from the subcortical-cortical emotion network, another network seems to function differently in depression. The default-mode network (DMN; Raichle et al., 2001) consists of a group of brain areas that shows negative BOLD responses during cognitively demanding tasks. It consists of hubs in the DMPFC, VMPFC, the posterior cingulate, inferior parietal cortex and parts of the temporal cortices including the hippocampal formation (Buckner, Andrews-Hanna, & Schacter, 2008; Sheline et al., 2009). This network has been

speculated to be involved in self-referential processing. Attenuated self-referential activity during effortful tasks may reflect an exhaustion of cognitive resources and may be critical for minimising interference from internal emotional states. The disturbed emotion regulation in depression and the overlap between brain areas associated with depression and the DMN, suggests a relation between this network and depression. Sheline et al. (2009) investigated the role of the DMN by asking participants to either passively view negative and neutral pictures or modulate the affective load of negative pictures into more positive or more negative. While the reappraisal of negative images resulted in lower activity in the DMN activity in healthy controls, it did not in depressed patients. Similarly, compared to healthy controls, Grimm, Boesiger, et al. (2008) found decreased negative BOLD responses in the DMN in depressed patients during emotion processing, which correlated with depression severity.

1.2.3 Environmental factors

Although depression is not necessarily triggered by environmental factors, these often do play a role. Especially stress induced by traumatic life events involving threat or loss, such as abuse or bereavement, seems to have a causal effect on depression onset (Kendler, Karkowski, & Prescott, 1999). But also job loss has been related to depression, partly mediated by financial strain (Price, Choi, & Vinokur, 2002). It must be noted that the relation between stressful events and depression onset is not necessarily of a causal nature. Depression itself can elicit stressful life events (Kessler, 1997) and individuals with a predisposition to depression are more likely to get involved in high-risk environments (Kendler et al., 1999). However, many studies have found a correlation between the manifestation of a negative life event and the subsequent onset of a depressive episode. This relation seems to be strongest for first lifetime episodes of depression (Monroe & Harkness, 2005).

Apart from stress caused by a negative life event, chronic stress has also been related to depression. One study found that chronic stress, compared to acute stress, was more strongly related to depressive symptoms (McGonagle &

Kessler, 1990). The findings of the study suggest that the effects of acute stress are diminished by chronic stress.

Another important environmental factor is constituted of social support networks (Holahan & Holahan, 1987). Within this factor especially the role of parents can be crucial. Studies have found a relation between a lack in care and low self-worth. Also, the causal attribution regarding a specific event made by a mother was predictive of the attribution made by her child. Moreover, judgements made by parents and their child regarding the competence of the child across a variety of domains seem to match up (Ingram, 2001). These findings suggest that disadvantageous cognitive processes can be transferred from parent to child and can eventually become internalised in offspring. There is also a higher prevalence of depression in individuals who have been brought up or are living in the city opposed to in a rural environment (Peen, Schoevers, Beekman, & Dekker, 2010). This has been attributed to differences in social environment and social stress processing. The latter was evident on a social stress task in which the amygdala showed dissimilar activation patterns in individuals living in cities compared to rural areas. The pgACC activation during this task also differed between individuals with a rural compared to city upbringing (Lederbogen et al., 2011).

1.2.4 A holistic view on the etiology of depression

While the factors related to depression have here been classified into three broad categories, none of these factors work in isolation. A complicated interplay of the different variables seems to mediate depression. For instance, the previously discussed negative self-schemata are thought to be formed during the early stages of life under the influence of harmful interpersonal relations and stressful life events. But these schemas can also become activated by negative events later in life (Beck, 2008). In addition, not every individual exposed to an adverse life event will end up developing depression, but those with a predisposition might. To complicate the relation between depression and negative life-events even further, research suggests that there is a positive correlation between genetic risk factors for depression and stressful life events

(Kendler et al., 1999). Moreover, the development of a depressive episode after an aversive life event will depend on an individual's response style as well. The relation between these various factors is thus neither clear-cut nor unidirectional.

What is also not clear is whether the disturbed balance between subcortical and cortical emotion processing areas are either the cause or consequence of negative self-schemata and other depressive symptoms. Regular neurotransmitter functioning was found to be affected by perceived uncontrollability over threats and restored after perceived control was maximised (Bandura, Taylor, Williams, Mefford, & Barchas, 1985). Similarly, maladaptive schema activation seems to be related to dysfunctional activity in the amygdala, ACC and medial prefrontal cortex (MPFC; Anand et al., 2005). It has been suggested that the formation of these schemas in depressed patients is linked to increased serotonin transporter binding which in turn results in decreased serotonin expression. This could either be a direct or indirect pathway mediating depression, the importance of which can be demonstrated by selective serotonin re-uptake inhibitors (SSRIs) that are designed to prolong the presence of serotonin in the synapse to alleviate depressive symptoms.

Phillips et al. (2003b) were amongst the first to describe the potential neural mechanism underlying depressive symptoms, based on their previously proposed ventral/dorsal emotion system model (Phillips, Drevets, Rauch, & Lane, 2003a). In this model, the ventral system is mainly involved in the production of affective states and the dorsal system with the effortful regulation of the ventral emotion system. The ventral system is comprised of the VLPFC, OFC, amygdala, ventral anterior cingulate gyrus, insula, thalamus and ventral striatum, the dorsal system of the DLPFC, DMPFC, dorsal anterior cingulate gyrus and hippocampus. Phillips et al. proposed that in depression hyperactivity in parts of the ventral system, in combination with volumetric reductions may result in a narrowing of the emotional range with negative bias as a result. In support of this Gotlib et al. (2004) suggested that hyperactivity in lower level emotion processing areas result in negative attentional bias and rumination. Disner, Beevers, Haigh, & Beck (2011) also integrated findings of abnormal

physiology with symptomology, focusing on Beck's cognitive model of depression. A similar mechanism underlying negative cognitive biases in depressed patients was identified, relating to dysfunctional coupling between the amygdala and DLPFC. The DLPFC has been implicated to regulate amygdala activity to for example emotional stimuli, yet the increased and prolonged amygdala activity in depressed patients indicates reduced top-down control. The involvement of the amygdala in emotional memories and emotional learning (Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; Phelps & Anderson, 1997) suggests that the amygdala plays an important role in the rumination tendency of depressed patients. Indeed, rumination has been implicated with sustained amygdala activation in combination with increased reactivity in the sgACC (Drevets, 2001). In addition, biased attention towards negativity has been associated with deficits in our attentional disengagement system, which involves the right VLPFC, DLPFC and superior parietal cortex. These areas show abnormal activity in depressed patients. Additionally, the rostral ACC, implicated in inhibitory processing, shows higher activity when disengaging from negative stimuli in depressed than healthy individuals, potentially demonstrating a requirement for larger cognitive efforts in this clinical population.

While many studies have investigated the neural correlates of negative cognitive biases, several studies have also examined the neural substrate of other depressive symptoms. Hypoactivation in the dorsal system has been related to impaired executive functioning (Austin, Mitchell, & Goodwin, 2001) and psychomotor slowing (Mayberg, 1997). The ventral system has been linked more closely to the somatic aspect of depression. According to the DSM-IV-RT a pronounced symptom of depression is anhedonia. The reward system with its (mesolimbic) dopaminergic projections, is likely to mediate anhedonia and the absence of behavioural incentive in depression (Drevets et al., 2008). Apart from reduced gray matter volume and cellular abnormalities in reward processing areas, reduced sgACC activity has been linked to reduced stimulation of mesolimbic dopamine release.

In sum, a complex interaction of factors seems to be at play in depression. Early adverse life events may, for example, result in the formation of maladaptive cognitive schematas. These can alter the way the environment is perceived and may even actively shape the environment in a perception-congruent manner. For instance, a child who continuously experiences rejection at home may expect similar reactions from peers and may interpret neutral comments in a negative light. This may lead to the crystallisation of negative self-schematas, thereby resulting in a vicious cycle maintaining depression. The difficulties with unravelling factors of cause and effect may be partly arising from dynamic relations between these factors. For example, the negative self-schematas in the example above seem to be both cause and effect, albeit at different stages. Research into depression thus far has identified an extensive range of factors involved and the importance of mapping these as accurately as possible to aid successful treatment. Longitudinal studies will be required to shed more light on the causal factors of this debilitating illness (Davidson, Pizzagalli, & Nitschke, 2009).

1.3 Treatment

Many different approaches have been taken up to treat depression, some more intrusive than others. Available treatment options can generally be classified as psychological, physical or pharmacological. Common psychological interventions include counselling and cognitive behavioural therapy (CBT; Beck et al., 1987). The aim of CBT is to modify the maladaptive cognitions and behaviour that depressed patients display. Initially a therapist instigates the examination of the validity of negative, irrational cognitions but eventually this self-questioning becomes internalised. The efficacy of various types of psychotherapy seems to be comparable, despite the somewhat different principles underlying each type (Ebmeier, Donaghey, & Steele, 2006). A benefit of psychological over pharmacological interventions is that patients learn adaptive coping strategies which can potentially prevent future relapse. As such they target the roots of depression rather than its symptoms. Although psychological interventions form the only group of available non-invasive

treatment, motivational deficits (or cognitive impairments) may hamper progress. Patients have to be willing to put in the effort to scrutinise each thought and action.

Physical interventions include ECT, repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS) and DBS. During the latter, electrodes are implanted in the subgenual cortical area, which then administer continuous electrical stimulation (Mayberg et al., 2005). Other neural targets have been used as well (see Schlaepfer & Bewernick, 2014 for an overview).

The last group is formed by the frequently prescribed anti-depressant medication. It has been found that 10-20% of all patients cannot tolerate the side-effects of their anti-depressant medication (Winans & Bettinger, 2004). As previously mentioned, a substantial percentage of depressed patients do not benefit from the currently available treatment methods. For instance 50-70% of all patients does not benefit from the first course of anti-depressant medication (Nelson, Delucchi, & Schneider, 2008; Rush et al., 2006). Anti-depresant medication can have high impact side-effects affecting sexual functioning, the gastrointestinal system and eating patterns (Khawam, Laurencic, & Malone, 2006), which can reduce the willingness of patients to take medication (Beck et al., 1987).

Fitting with the conception that depression arises due to the complex interplay between a variety of factors, treatments that directly affect the various components of depression may yield the largest clinical improvements. This is supported by the finding of some studies that a combination of an antidepressant drug with psychotherapy has a superior treatment effect on depression compared to either treatment alone (Blackburn, Bishop, Glen, Whalley, & Christie, 1981; Keller et al., 2000, but see for instance De Jonghe et al., 2004 for an opposing view). It thus seems that neurofeedback training offers important advantages over conventional treatment methods. To judge the potential worth of neurofeedback training as an add-on treatment for depression, this thesis investigated the mechanisms via which neurofeedback could alleviate depression.

Chapter 2 – fMRI-based neurofeedback training

The behavioural effects that neurofeedback training can induce have been under investigation since the finding that feedback information from autonomic measures, such as heart rate, can be used to attain some form of control over these measures. The vital component of neurofeedback training is the provision of feedback information contingent on one's performance, which then aids to shape the set of attempted cognitive strategies in the direction that fit the task requirements best. The continuously updated feedback mapping one's performance has an embedded reward (and punishment) component, which can be expanded with more explicit forms of rewards such as monetary incentives (Bray, Shimojo, & O'Doherty, 2007). As such, neurofeedback training operates along the principles of operant conditioning, which is the process through which an individual learns to produce a desired outcome guided by punishment and reward (Skinner, 1937). The outcome of operant conditioning has traditionally consisted of the generation of a particular kind of overt behaviour. Due to the development and improvement of brain imaging techniques, a particular brain state can now be chosen as the ultimate goal of the conditioning process as opposed to a certain type of behaviour. The administration of this biofeedback procedure with brain activation measures was initially delivered via electroencephalography (EEG), which was administered to treat for instance epilepsy but also depression (Baehr, Rosenfeld, & Baehr, 1997; Sterman & Friar, 1972). In depression, feedback from the frontal brain regions was provided to acquire control over the frontal activation asymmetry (see section 1.2.2). Although patients with mild depression have shown improvements after a course of EEG feedback (Choi et al., 2011), its effectiveness in more severely depressed patients remains to be seen. One crucial limitation of EEG is its poor spatial resolution, which excludes the possibility to convey activation feedback from subcortial structures that have been shown to be critical in depression. While functional magnetic resonance imaging (fMRI) systems have the spatial resolution that EEG lacks, only relatively recently it became a useful tool to deliver neurofeedback. One criterion for operant learning to occur is namely that the reward (or punishment) should follow shortly after the wanted (or

unwanted) behaviour occurs (Staddon & Cerutti, 2003). Rapid technological advances resulted in the development of real-time fMRI (Cox, Jesmanowicz, & Hyde, 1995), which allows the online processing of fMRI data. This has resulted in applications such as brain-computer interfaces (BCIs; Sitaram et al., 2007), the ability of online data quality control (Bagarinao, Nakai, & Tanaka, 2006) and in the opportunity to deliver neurofeedback training from spatially confined areas. Although the real-time processing of fMRI data ensures that feedback can be provided within a few hundred milliseconds after the imaging data has been obtained, there will still be a delay of 4 – 8 s between changes in neural activity and changes in the feedback signal due to the haemodynamic response delay. This does not negatively affect the learning process as this lag is consistent and participants can learn to account for it (Sulzer, Sitaram, et al., 2013).

Neurofeedback training has allowed the development of a completely new field of research. Traditional neuroscience experiments have asked participants to conduct a task so the brain activity that fluctuated as a function of this task could be measured as the dependent variable. In essence, neurofeedback permits the parametric modulation of brain activation thereby approaching brain activity as an independent opposed to dependent variable. The technical requirements for delivering neurofeedback training will be shortly discussed below, followed by an overview of relevant neurofeedback studies conducted so far.

2.1 Technical background

2.1.1 MRI

Magnetic resonance imaging (MRI) allows the visualisation of hydrogen spins by applying various magnetic fields. The protons of hydrogen nuclei within the brain (and body) normally spin around their axis in random directions and with a random frequency. When these protons are exposed to a static magnetic field (B_0) in an MRI scanner all protons align with the direction of B_0 in either a

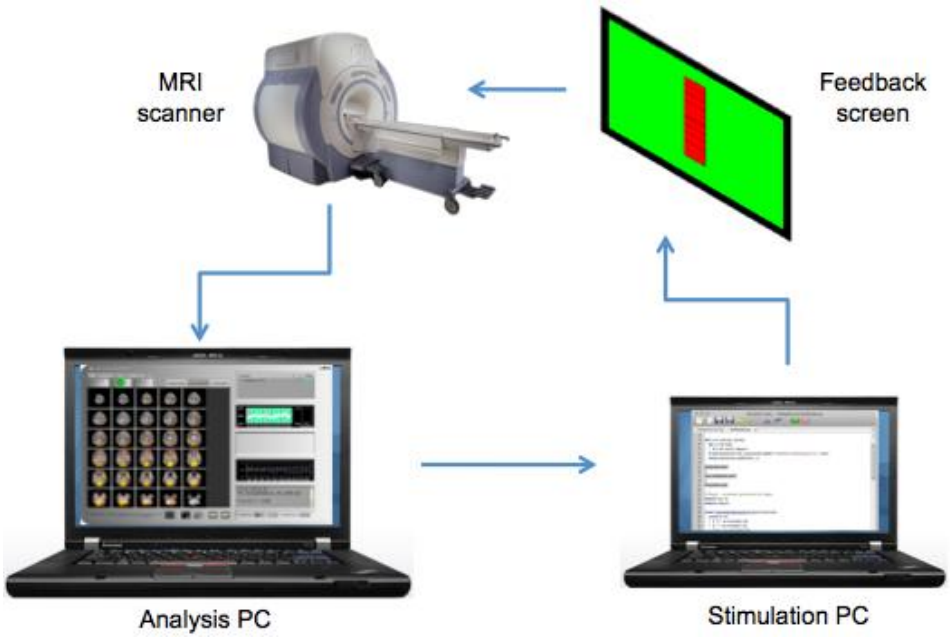

Figure 1.1. Main components of fMRI-based neurofeedback setup. Participants conduct a task related to the role of the target area in the scanner while the obtained brain images are analysed in real-time. Activation values are then transformed into a simplified display that is fed back to the participant in the scanner.

parallel or anti-parallel fashion. The magnetic forces of these two alignment states cancel each other out, but because slightly more protons align in a parallel fashion a net magnetization vector (M_z) longitudinal to the static magnetic field arises. The protons will also start to precess around the magnetic field lines of the static magnetic field with a frequency dependent on the magnetic field strength. This frequency is called the Lamor or resonance frequency. Images are then created by temporarily applying a RF pulse at the resonance frequency of the protons. An RF wave can transfer energy to protons which causes the protons to precess in phase, thereby establishing a transversal magnetization. In addition, more protons will become aligned in an anti-parallel fashion, thereby reducing M_z. As soon as the radio-frequency (RF) pulse is switched off the protons will start to dephase because of spin-spin interactions that are a consequence of the uneven distribution of the magnetic fields of neighbouring protons. This causes the transversal magnetization to disappear, the time constant describing the speed of this process is called the transversal relaxation time T2. Additionally, the protons that became aligned in the anti-parallel state will release the absorbed energy thereby returning to the parallel

alignment and reinstating the initial M_z. The speed of this process is called longitudinal relaxation time and is termed T1. The signal decay occurring due to a combination of spin-spin interactions and magnetic field inhomogeneities is term T2* relaxation. The intensities of the signals can be computed via the Fourier transformation, via which brain images can be reconstructed (Schild, 1990).

FMRI systems measure brain activity indirectly by relying on the blood oxygenation level dependent (BOLD) effect (Ogawa, Lee, Kay, & Tank, 1990), which is based on the neurovascular coupling mechanism. In essence, fMRI picks up changes in signal arising from differences in magnetic properties of oxygenated and deoxygenated haemoglobin and hence is able to discriminate between active and non-active brain areas (Huettel, Song, & McCarthy, 2004). Deoxygenated haemoglobin is paramagnetic and distorts the magnetic field resulting in a relatively faster dephasing of magnetised proton spins in the fMRI scanner. Oxygenated haemoglobin is diamagnetic and results in a relatively slower dephasing of magnetised proton spins thereby leading to an increase in fMRI signal. Activated brain regions require an increase in oxygen supply from haemoglobin which will be catered for by an increase in cerebral flood flow (CBF) and cerebral blood volume (CBV). This increases the presence of oxygenated compared to deoxygenated blood, thereby resulting in an increase in BOLD signal.

2.1.2 General setup

The information measured via the MRI system is used within the neurofeedback procedure (Figure 1.1). Apart from this system, important components of a neurofeedback system based on real-time fMRI data are data acquisition and acquisition time, computational power, online pre-processing such as smoothing but also motion correction and realignment, online data analysis, feedback modality and presentation, region-of-interest selection and participant instruction. In this closed-loop system, the participant in the MRI scanner engages in different mental strategies based on initially provided instructions relating to the function of the selected ROI. Due to recent technical

developments it is now also possible to provide feedback from pattern classification algorithms, thereby training participants to control networks opposed to isolated brain areas (Caria, Sitaram, & Birbaumer, 2012). The imaging data from the ROI or brain pattern is then imported to an analysis computer that performs essential pre-processing steps and computes for instance an incremental general linear model (GLM). The analysed data is then forwarded to a stimulation computer that transforms the raw activation values into feedback screens that can be easily interpreted by the participant in the scanner. This allows a trainee to test a variety of strategies to influence his or her brain activity in the desired direction. The sensitivity of feedback can be adjusted to promote shaping, i.e. guiding the trainee towards desired strategies by initially rewarding even small activation changes in the aimed direction and progressively increasing task difficulty (Weiskopf et al., 2005)

2.1.3 Current setup

A General Electric (GE) 3T MRI scanner was used to acquire imaging data at the Cardiff University Brain Research Imaging Centre (CUBRIC). Functional images were obtained in the AC-PC plane via echo-planar imaging (EPI) sequences (TR = 2000 ms, TE = 35 ms, 30 slices, FA = 80, FOV = 192 x 192, matrix size = 64x64, slice order = interleaved, inplane resolution = 3 mm x 3 mm, slice thickness = 3, gap thickness = 1). The first six volumes were discarded to account for T1 equilibrium effects.

Turbo-BrainVoyager (TBV; Brain Innovation, Maastricht, The Netherlands) accessed the folder in which acquired brain volumes were saved by the scanner to calculate an incremental GLM. TBV performed spatial smoothing (4 mm) and online motion correction. The translation and rotation parameters were saved and used in the offline analysis. TBV calculated and outputted an activation value of the top-third voxels in the target area, which was accessed by PsychoPy (Peirce, 2007). The neurofeedback task in the depression study (see Chapter 5) consisted of four loops of an up-regulation condition for 20 s and a rest condition for 20 s. In the rest condition PsychoPy calculated percent signal change (PSC) by first calculating a baseline by averaging the activation

values of the last five volumes. Temporal smoothing was induced via this sliding window approach. An activation average was then calculated over the last three volumes via a similar sliding window approach. PSC was then calculated via the formula below.

$$PSC = \frac{\text{(Activation average – baseline average)}}{\text{Baseline average}} \times SF$$

With SF being the shaping factor, which was a value between 8100 and 22500. The exact value selected for SF depended on patient performance and estimated performance differences between both groups.

During the up-regulation condition in the depression study the activation average was computed in the same way, but the baseline average represented the average of the activation values of the last five volumes during rest. A green background with an arrow pointing upwards signalled the up-regulation task and a yellow background with a downwards pointing arrow signalled the rest condition. During the green background participants were asked to increase the activation in their target area as much as possible via mental imagery. During the yellow background participants were instructed to lower the activation in their target area as much as possible by counting backwards from 99 in steps of three. Each TR PsychoPy adapted the number of red blocks on the thermometer dial accordingly with an empty thermometer dial reflecting PSC <10, one red block reflecting $10 \leq PSC < 20$ and the maximum 10 blocks representing PSC > 100. The thermometer display was projected on a screen behind the participant's head and was viewed via a mirror fitted to the head coil.

During the neurofeedback runs respiratory rate was recorded via a respiratory belt and heart rate via a finger pulse sensor. In-house MATLAB (Mathworks Inc) scripts compiled by Dr Kevin Murphy at CUBRIC (Cardiff University Brain Research Imaging Centre) were used for quality control and to compute the average heart rate (HR) and respiration volume per time (RVT) during each obtained volume. These were then included as covariates in the GLM model.

2.2 Control group design

Control group type	Task strategies		Scanner	Feedback		Controls for		
	Comparable	*Related*		*Inaccurate*	*Accurate*	Scanner experience	Task-specific effects	Success rate
A	x						x	
B	x		x			x	x	
C	x		x	x		x	x	x
D		x	x		x	x		x
E		x	x		x	x		

Table 2.1. Overview of control group types and characteristics available to fMRI-neurofeedback studies.

The design of a control group appropriate for the particular topic under investigation poses a major challenge for neurofeedback studies. No single control group type is superior to others and each type has its own strengths and weaknesses. In neurofeedback, participants assigned to the control group generally execute the same task as those in the experimental group, albeit under different circumstances. Control groups can either go in the MRI scanner or not, can receive feedback or not and the latter can be accurate or not. Inaccurate feedback could be feedback from a previous participant, inverted feedback or feedback from a region unrelated to the task described to the participant. Control groups outside the MRI scanner (Table 2.1, type A) control for any behavioural (or clinical) changes caused by (repeated practise of) the task itself opposed to increased brain activation. In clinical trials, such a control group would also control for symptom improvements induced solely by patient expectations arising from taking part in a clinical trial. A major drawback from control groups outside the MRI scanner is that brain activation cannot be compared across groups. A major disadvantage of not providing any feedback (Table 2.1, type A/B) is that success rate between groups is not matched. The largest disadvantage of providing inaccurate feedback (Table 2.1, type C) is that the non-contingency of the feedback signal may result in frustration, diminished motivation and supposition of control group assignment. An exception occurs when the inaccurate feedback originates from an area unrelated to the task, in which case the control group does not control for

success rate. A shortcoming of providing accurate feedback from an area unrelated to the topic of interest (Table 2.1, type D) and setting participants a task that influences that particular area, is that behavioural (or clinical) group differences might be due to differences in target area activation or task strategies. The careful selection of a control area is required as "unrelated" areas might still affect the area of interest indirectly. One could also present the control group with a related task and ongoing activation changes without asking the participant to influence these activation levels (Table 2.1, type E). This control group allows a more direct investigation of the importance of self-induced versus externally induced brain activation changes, yet requires careful matching of visual input. In addition, it does not control for reward rate. As there is no one perfect control group, one solution may be including a multitude of control groups, but this would have undesirable implications such as increased sample size and costs.

2.3 Review of neurofeedback studies

The number of studies applying real-time fMRI to administer neurofeedback has increased dramatically over the last decades. A wide variety of regions has been targeted, ranging from motor areas (Berman, Horovitz, Venkataraman, & Hallett, 2012; Bray et al., 2007; DeCharms et al., 2004; Hampson et al., 2011; Papageorgiou, Curtis, McHenry, & LaConte, 2009; Weiskopf et al., 2004; Yoo, Lee, O'Leary, Panych, & Jolesz, 2008; Yoo & Jolesz, 2002) to auditory areas (Yoo et al., 2006, 2007), visual areas (Scharnowski, Hutton, Josephs, Weiskopf, & Rees, 2012) and higher cognitive processing areas such as the rostrolateral anterior prefrontal cortex (McCaig, Dixon, Keramatian, Liu, & Christoff, 2011), the parahippocampal place area (Weiskopf et al., 2004) and orbitofrontal cortex (OFC; Hampson et al., 2012). Several studies have investigated the effect of the self-regulation of areas implicated in emotion processing, including the anterior cingulate cortex (ACC; Weiskopf et al., 2003) and amygdala (Zotev et al., 2011). Zotev et al. instructed healthy participants to use the contemplation of positive autobiographical memories in order to up-

regulate the activity in the amygdala during neurofeedback runs. The control group that had been shown feedback from the horizontal segment of the intraparietal sulcus (HIPS) and that had received the same task instructions did not show the ability to increase BOLD activity in the amygdala like the experimental group did. Veit et al. (2012) showed subjects threat-related pictures while presenting neurofeedback signals originating from the anterior insula, which participants had to up- and down-regulate. Although subjects managed in the up-regulation task, this was not the case for the down-regulation task. The authors suggest that monitoring the poor performance during the down-regulation condition may have resulted in increases in activation as an unwanted by-product. While most studies selected their target area based on anatomical criteria, it is also possible to select individually tailored target areas via a functional localiser. Johnston, Boehm, Healy, Goebel, & Linden (2010) identified the brain region most responsive to negative emotions, via pictures from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1997), on an individual basis and asked individuals to attempt up-regulation by using affective imagery or memory recollection. All participants used the imagery or recollection of negative emotions to increase the activity in the target area which were generally in the insula, VLPFC or medial temporal lobe (MTL). Another study adopted the same approach but focused on positive emotions and established the feasibility of the up-regulation of areas implicated with positive mood (Johnston et al., 2011). In a study by Lawrence et al. (2013) participants were free to use positive or negative arousing memories to increase the activation in the right anterior insula. Even the feasibility of volitional down-regulation of sgACC activity has been demonstrated (Hamilton, Glover, Hsu, Johnson, & Gotlib, 2011). Positive affective strategies were successful to achieve down-regulation in the experimental group, which is noteworthy considering its implicated role in emotion generation, but not in the control group that received yoked feedback from previous participants.

In several of these studies self-regulation of brain activation was accompanied by behavioural changes. Rota et al. (2009) for example described that a voluntary enhancement of activity in the pars triangularis of the right IFG

resulted in improved accuracy on a task involving the classification of emotional prosodic intonations. Similarly, aversive pictorial stimuli were more negatively rated on valence when participants up-regulated the activity in the anterior insula, via recalling positive and negative events, compared to during a rest period (Caria, Sitaram, Veit, Begliomini, & Birbaumer, 2010).

Studies have not only investigated the effects of neurofeedback on behaviour, but also on cerebral reorganisation (Lee et al., 2011). Four neurofeedback sessions (executed in one day) involving insular up-regulation resulted in a more spatially confined recruitment of areas implicated with emotion and learning. Activation levels increased during early sessions in areas mediating learning, such as the ACC and dorsolateral prefrontal cortex (DLPFC), but decreased during later sessions. Activation in task-related areas, such as the insula, on the other hand increased over the sessions. This suggests that a combination of pruning and connection strengthening mediates neurofeedback performance.

After the feasibility of the volitional control over confined brain areas had been established, the first applications of neurofeedback in a clinical setting were tested. DeCharms et al. (2005) for instance found that healthy participants were able to engage in the effortful regulation of the rostral ACC (rACC), an area presumed to be involved in pain processing. This modulated their percept of a noxious thermal stimulus applied to their palm. Next, a group of chronic pain patients was trained with neurofeedback from the rACC. Whenever their volitional up-regulation enhanced the activity in the rACC, increased pain intensity levels were reported. Conversely, down-regulating this area was accompanied by a decreased experience of pain. Importantly, this effect did not show for control groups that either received no feedback, received feedback from another participant's rACC, or received feedback from another - not targeted - brain region. It thus seems that participants are unable to figure out an effective strategy if they receive no, random or unrelated feedback information and that the successful regulation of brain activity does not merely occur because of repeated practice or anticipated pain perception. A significant correlation between the activation increase in the rACC and pain rating were

found in the group of chronic pain patients. Neurofeedback has also been found to induce a clinical improvement in Parkinson Disease (Subramanian et al., 2011). Up-regulation of the supplementary motor complex was accomplished by motor imagery and was paralleled by an increase in finger tapping speed and a reduction of clinical motor symptoms.

Applications of neurofeedback training in clinical settings have also involved mental illnesses. In 12 training sessions spread over two weeks, Ruiz et al. (2013) asked schizophrenic patients to increase the activation level in their bilateral insula while being provided with neurofeedback information. Patients managed to achieve volitional control over their brain activity via the recall and imagery of emotionally affective events. Given the impairments in the recognition of emotional expressions that are commonly noted in schizophrenia, patients interestingly demonstrated improved accuracy in recognising disgust after neurofeedback training. However, this was coexistent with a lowered accuracy in recognising happy facial expressions. Connectivity analysis showed an enhanced connectivity between the insula, medial prefrontal cortex and amygdala, areas postulated to play a key role in the regulation of emotions. Only two studies so far have administered neurofeedback training to depressed patients (Linden et al., 2012; Young et al., 2014). In a proof-of-concept study, Young et al. (2014) selected the left amygdala as a target area for the experimental group as it has shown a reduced response to positive stimuli in depression which is inversely correlated with depression severity. A control group was included which received feedback from the HIPS and both groups were instructed to use the recall of positive autobiographical memories to induce an increase in activation in their target area. During the neurofeedback session, the left amygdala was significantly up-regulated in the experimental group, but not in the control group. This showed that accurate feedback was crucial to achieve up-regulation of the left amygdala and that merely engaging in the recollection of positive memories did not have a similar effect on its activation levels. This study assessed short-term changes in mood and found that the pre-post scan decreases in anxiety and increases in happiness were only significant in the experimental group. It must be noted however that since the HIPS is implicated with number processing, patients in the control group were

not successful in up-regulating their target area via positive memory recollection. Consequently these patients did not receive the same amount of positive feedback as patients in the experimental group, which may have had a confounding effect. In addition, there was a significantly higher number of co-morbid diagnoses in the control group, which has been associated with lower remission rates in a clinical trial investigating the anti-depressant effect of citalopram (Trivedi et al., 2006). In Linden et al. (2012) the target areas were selected on an individual basis based on the responsiveness to positive affect. This was determined by a functional localiser consisting of positive, negative and neutral IAPS pictures. Patients were aware of the selection criterion of the target area and were instructed to use positive emotion imagery or recall to induce an increase in activation in that particular area. During three neurofeedback runs, which lasted seven minutes each, 20 seconds of this up-regulation condition were alternated with 20 seconds of rest. During both conditions patients received neurofeedback in the format of a thermometer display and patients were aware that changes on this display reflected alterations in the activity level of the target ROI. After four weekly neurofeedback sessions all patients were able to significantly up-regulate the target area, with improvements in up-regulation ability already noticeable between the runs of the first session. Patients adopted a variety of strategies to achieve the up-regulation, which ranged from the imagery of out-of-body experiences to the recollection of family holidays. Hamilton Depression Rating Scale (HDRS) scores were obtained before and after the neurofeedback course and were significantly decreased upon completion of the study. Moreover, a positive correlation was found between the improvement in up-regulation over sessions and improvement on the HDRS. The control group that took part in an equal number of sessions of a comparable positive emotion imagery task, outside the scanner and without any feedback, did not show any change on the HDRS. Given the fact that each group only contained eight patients, future studies adopting larger, blinded, randomised trials will be required to confirm these findings.

To summarise, many applications of real-time fMRI have been developed over the last decades, including online data quality control and neurofeedback

training. The latter offers the exciting opportunity to modulate brain activation levels as an independent variable, thereby offering important insights in brain-behaviour relationships. The potential worth of neurofeedback training for the treatment of psychiatric illnesses has increasingly been recognised, given the non-invasive manner to interfere with dysfunctional brain activity. The exact contribution that neurofeedback training can make in this context will need to be investigated in large controlled studied.

Chapter 3 - Emotion regulation via neurofeedback training to improve symptoms of depression

The abnormal brain and cognitive processes associated with depression have been set out in Chapter 1. The ability of neurofeedback training to modify (abnormal) brain activation in a non-invasive manner has been described in Chapter 2. As previously described, the high prevalence of depression in combination with the limited effectiveness of currently available treatment options asks for the development of a novel treatment method. This chapter will present the rationale behind applying neurofeedback training to alleviate depression via two models of emotion regulation.

Although many aspects of depression are still elusive, studies into affective disorders agree that the successful regulation of one's mental state is vital to maintaining, or establishing, one's emotional well-being (Amstadter, 2008; Gross & Thompson, 2007; Taylor & Liberzon, 2007). The working definition of emotion regulation as adopted in this thesis will refer to the processes via which the termination of undesired emotional states as well as the achievement and maintenance of desired emotional states can occur (Carstensen, Pasupathi, Mayr, & Nesselroade, 2000; Gross, Richards, & John, 2006; Larsen, 2000). The two pathways mediating emotion regulation that are explored in this thesis are cognitive and physiological self-regulation.

3.1 The multimodel system of emotion activation and regulation

Izard (1993) proposed a multimodel system of emotion activation consisting of a sensorimotor, motivational, neural and cognitive system. Each of these can also serve as an emotion regulation system (Izard and Kobak in Izard, 1993). The neurofeedback task employed to alleviate depression (see section 2.1.3 and section 5.3.3) is based on Linden et al. (2012) and offers a dual pathway to improve symptoms of depression. First of all, neurofeedback could induce changes in the neural system, albeit interpreted in a slightly different manner

than Izard proposed. Izard described the neural system to function independently from cognition, which would for instance be the case during electrical stimulation of the brain. Neurofeedback targets the neural system in a less direct manner via cognition. Apart from a few brain areas that serve a main role in memory processes or basal biological functions, most brain regions showing a deviant activation pattern in depression are involved in emotion processing. This plethora of brain areas provides for a wide range of suitable targets for neurofeedback training. The successful execution of the neurofeedback task via appropriate cognitive strategies will then result in changes in brain activity, thereby targeting the biological substrate that may mediate the depression. Clinical improvement of depression resulting from for instance CBT, DBS or anti-depressant medication has been associated with alterations in brain activation that are somewhat distinct for the different treatment types (Goldapple et al., 2004). CBT-induced changes can be seen as more of a side-reaction occurring due to modified cognitive strategies than as the deliberate restoration of the abnormal neurobiology of depression. While conventional pharmacological treatment and surgical procedures that aim to target this underlying physiology are invasive and can have severe side-effects, neurofeedback has been established to be safe to administer (Hawkinson et al., 2012).

Second of all, neurofeedback training has the potential to alleviate depression via inducing modifications in the cognitive system that Izard (1993) described. As mentioned in section 1.2.1, perceived thought control efficacy can be expected to form a crucial factor in the process of emotion regulation. The chance of someone attempting to regulate his or her emotions seems dependent on the person's estimate of how successful an attempt to terminate unwanted emotional states and/or acquiring desired emotional states will be. Low levels, or absence, of perceived thought control efficacy as found in depression can be experienced as dejecting for several reasons. The inability of thought control can cause feelings of helplessness and despair, may create stress by affecting one's concentration and performance, may lead to prolonged exposure to traumatic contents and can cause worry about one's ability to refrain from acting on thoughts relating to activities involving a taboo (Bandura, 1997).

Acquiring a sense of thought control may not only reduce the frequency with which intrusive thoughts occur but can also affect the intensity and acceptability of these thoughts, thereby reducing any feelings of powerlessness or helplessness (Rehm, 1977). Because depressed patients will have to use positive emotion imagery to exercise control over their emotion network, neurofeedback also targets the cognitive component of depression. During neurofeedback training patients can directly see whether their efforts are paying off, a feature that psychological treatments such as cognitive behaviour therapy are lacking, at least at this level of immediate feedback. The motivational problems that are concomitant with depression can consequently hamper improvements during for instance a CBT course, yet neurofeedback may bypass this obstacle providing an important advantage. When the strategies underlying these immediately perceptible short-term yields crystallise after sufficient training, longer-term improvements can be expected. The various ways of executing thought control in general will be described next, followed by an explanation of how neurofeedback can contribute to the acquisition of these regulation skills.

3.2 The process model of emotion regulation

The thought control pathways, via which one can regulate affect, described by Bandura predominantly depend on attention regulation. However, emotion regulation can also be achieved via other routes which are set out in Gross's process model of emotion regulation (Gross, 1998). According to this model, emotion regulation can occur at each stage of the emotion generation process. The first type occurs when a situation, either imaginary or real, is selected. This situation can be constituted by an object, place, activity or person. At the second stage a selected situation can be modified to regulate one's emotion. This occurs if one draws closer or further away from the situation. At the following stage in the emotion generation process one pays attention to the situation. Hence emotion regulation can occur by shifting one's attention to particular aspects of the situation, as extensively described by Bandura. Gross

distinguishes between three forms of attentional deployment: concentration, rumination and distraction. The boundaries between these forms are not always clear and may blend into each other. Generally, while concentration is about focusing all cognitive resources available to a certain aspect of a situation, distraction is about attending away from (distressing aspects of) the situation to limit the influence of emotionally evocative aspects. Repeatedly revisiting a particular situation forms the key element of rumination, which involves inward-directed attention. At the forth stage of emotion formation one appraises the situation. Effectuating a cognitive change can alter one's affective state at this point. Common examples are reappraisal, a process that involves changing the interpretation of an affectively charged stimulus in such a way that changes the emotional impact, and acceptance. At the fifth stage one produces a response, the modulation of which would equal emotion regulation as well. Response suppression is a well-known form of this type of affect regulation. The stages in the process model of emotion regulation are recursively revisited while the emotional state increases in intensity. By definition of a model, the process model provides a simplified representation of emotion regulation. It does for example not illustrate the effect that response modulation can have on the preceding stages. Nevertheless some specific predictions arise from this model that can be empirically tested. For instance, the model predicts different levels of memory recollection after distraction, reappraisal and suppression. Distraction is an emotion regulation strategy that occurs relatively early in the emotion generation process, during which the situation will not have been encoded properly. Reappraisal requires more elaborate processing of the affective meaning of the situation as compared to distraction and should thus result in enhanced memory performance. This prediction is supported by findings showing superior memory recollection for reappraised information (Dillon, Ritchey, Johnson, & LaBar, 2007; Richards & Gross, 2000; Sheppes & Gross, 2011) and impaired memory performance for information viewed during distraction (Sheppes & Meiran, 2007). Although suppression occurs relatively late in the process of emotion generation, it requires the active inhibition of situation-related memories. It has indeed been found that the employment of suppression results in reduced memory performance (Richards & Gross, 1999). The process model also predicts differences in sympathetic arousal. While

reappraisal occurs before a certain emotion has reached its maximum intensity and before it has been expressed at a behavioural level, suppression requires modifications once the expression of a certain emotion occurs. Confirming this prediction, emotion suppression has been found to increase cardiovascular activation, while reappraisal did not result in physiological changes (Gross, 1998; Richards & Gross, 1999).

3.3 The acquisition of adaptive emotion regulation via neurofeedback training

Neurofeedback could aid the development of thought control in several ways. In the first instance, the objective and specific feedback that participants receive could foster trust in patients that thoughts can actually be subjected to volitional control. Once this initial hurdle is taken participants can learn how to improve their thought control skills. It is important that this process is guided by objective feedback, as it is possible that depressed patients do not have an accurate idea of which thoughts evoke the most happiness. It is highly unlikely that false feedback can be as effective. It does not target the biological substrate of depression and patients are likely to notice the incoherence between strategies and feedback when a certain strategy works the one moment but not the other. As a result of accurate feedback, the perceived self-efficacy of patients is likely to increase, thereby increasing the likelihood of the initiation and continuation of thought control processes. During the proposed neurofeedback task depressed patients will receive neurofeedback from an area involved in the processing of positive emotions and will be asked to increase the activity level as much as possible. To successfully carry out the task participants will have to use positive emotion imagery or recollection. This strategy initially targets the first stage as described in Gross's model as it requires the generation of an internal situation with desired attributes. The focus of the neurofeedback task then shifts to the third stage of the model, which is an attractive target for reasons discussed below, as patients will reminiscence over the positive situation. So instead of employing emotion regulation to alter one's

affective state as is generally the case, it will be used to maintain a desired affective state. Although rumination is generally discussed in a negative context one can also ruminate on positive emotions, a concept that has been termed savoring (Bryant & Veroff, 2006). Aldao, Nolen-Hoeksema, & Schweizer (2010) compared the relation between different emotion regulation types and depression and found the strongest relation between depression and rumination. Based on this finding it is surprising that most conventional cognitive therapies focus on reappraisal strategies, as it suggests that the ruminative response styles that depressed patients often engage in (Nolen-Hoeksema et al., 2008) may be employed in an advantageous manner. Rumination may namely come more natural to patients than reappraisal and may therefore have enhanced effectiveness. Via passing through the stages of Gross's model, the neurofeedback task allows patients to build up a repertoire of positively framed situations that can replace unwanted, intrusive situations that may have become embedded in a patient's mind due to, for instance, rumination and a lack of inhibition to negative material (Joormann & Gotlib, 2010). It is important to note the difference between the self-regulation strategy required in this task and the less adaptive strategy of distraction (Wenzlaff & Wegner, 2000). The proposed neurofeedback task requires the production of desired thoughts, which may potentially result in distracting oneself but only as a by-product opposed to as a sought-after outcome.

There are several reasons why the third stage of the process model is an attractive target in combating depression. First of all, there is a lot of evidence showing maladaptive attention processes in depressed patients, which seem to mediate depression (see section 1.2.1). Moreover, these dysfunctional attention processes seem to outlast the depressive episode and can increase the risk of relapse (Wadlinger & Isaacowitz, 2011). Secondly, findings show that training one's attentional focus is very feasible. Attentional plasticity has been found across a wide spectrum of ages (Bherer et al., 2005), as well as in children with attention deficit hyperactivity disorder (ADHD; Kerns, Eso, & Thomson, 1999). This suggests that the concentration deficits that depressed patients are likely to suffer from will not impede emotion regulation training. Using attentional shifts in relation to affective stimuli has also been shown to be

feasible (Derryberry & Reed, 2002; MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002). Thirdly, it seems that depressed patients are unaware that attentional resources can be deployed to regulate emotions (Mohlman, cited in Wadlinger & Isaacowitz, 2011). Fourthly, any induced attentional shifts seem to be enduring. Rothbart, Ziaie, & O'Boyle (1992) have found that repetitively focusing attention towards or away from certain stimuli can result in these attentional shifts becoming automatic. The last reason is related to the stage of the emotion generation process at which attention plays a role. Gross grouped the first four stages under the umbrella term antecedent-focused emotion regulation and classified the fifth stage as response-focused emotion regulation. It has been postulated that emotion regulation is less effortful during early stages of the emotion formation, thereby making attentional deployment a suitable candidate. In addition, acquiring emotional control at this stage may facilitate achieving control at later, more challenging, stages. Targeting these later stages straight away is less likely to be successful given that cognitive resources in depressed patients can be compromised.

In summary, fMRI-based neurofeedback seems to have the required attributes to become a valuable tool in the treatment of depression by offering an individualised treatment approach via both bottom-up and top-down mechanisms. It seems to provide the opportunity to target the multitude of brain areas implicated in depression in a non-invasive way that does not induce any side-effects, thereby restoring the abnormal neurobiology underlying depression. At the same time neurofeedback training could increase the low level of perceived self-efficacy that is associated with depression and that appears to be a crucial component in the formation, maintenance and recurrence of depression. Neurofeedback thus seems to offer the holistic approach that conventional pharmacological, physical and psychological treatment methods are lacking and that may have brought about the currently daunting battle against depression.

Chapter 4 - Self-regulation of higher visual processing areas using real-time fMRI neurofeedback

4.1 Abstract

It is common for neurofeedback studies to include a control group that receives yoked feedback, for instance originating from a previous participant. However, the design of an apt control group in neurofeedback studies employing mood paradigms is more challenging, especially in a clinical population. The frustration that patients may experience as a result of detecting the non-contingency of sham feedback, renders this type of control group unsuitable for a study investigating the potential of neuroimaging feedback in alleviating symptoms of depression. The current study therefore investigated the feasibility of a control area in the parahippocampal place area (PPA), a brain area involved in the processing of scenes, by training healthy volunteers to up-regulate their PPA activation. To increase specificity, participants received differential feedback from the PPA and fusiform face area (FFA), both areas involved in higher order visual processing and activated during the imagery of scenes and faces respectively. It was found that all participants were able to increase PPA activation with respect to FFA activation by imagining scenes, but not faces. This did not seem to affect bistable perception on a binocular rivalry task nor the accuracy and reaction time on a perceptual task involving judgements of faces and scenes, although both tasks may have lacked sensitivity. Given the possibility of PPA self-regulation and the apparent absence of perceptual changes resulting from this, a control group receiving valid neurofeedback training from the PPA was included in the neurofeedback and depression study described in Chapter 5.

4.2 Introduction

One of the fundamental topics studied in neuroscience is the relation between brain activation and behaviour. The domain of visual perception is pre-eminently suitable for exploring this topic given the objective measures available to study this field. Many studies have used these to correlate behavioural changes with changes in brain activation. The results of such research do not allow drawing inferences of causality. Any observed changes in brain activation could namely have been caused by the experimental manipulation and may play no causative role in the cognitive function studied (Silvanto & Pascual-Leone, 2012).

Studies employing transcranial magnetic stimulation (TMS) can influence brain activation directly and are more suitable to study causality in brain-behaviour relations. In the visual domain, binocular rivalry (BR) paradigms have often been used to investigate this relationship. Under regular perception conditions, our left and right eye receive slightly dissimilar input from the exact same scene due to the angle under which each eye views the scene. The input from both eyes is projected onto the same spot on the retina, from where our brain solves the incoherence to create the unified view we constantly perceive. A special instance of this process occurs when an irreconcilable view is presented to our eyes, i.e. a different image to each eye, and BR occurs. During BR the two images rival for conscious awareness as our brain is unable to resolve the discrepancy between both eyes. It has been suggested that BR is a relatively automatically occurring process, although it must be noted that some studies have shown that it can be subject to voluntary control (Chong, Tadin, & Blake, 2005). Pearson, Tadin, & Blake (2007) showed that single-pulse TMS administered over the occipital cortex increased the number of perceptual alternations in a BR paradigm. Carmel, Walsh, Lavie & Rees (2010) found that inhibiting activation in the right superior parietal cortex with low-frequency TMS resulted in shortened BR dominance durations. It thus seems that a combination of bottom-up and top-down mechanisms give rise to conscious visual perception, yet the exact interplay between both is still unclear.

Another way of directly influencing brain activation levels in visual processing areas and assessing perceptual changes arising from this is called functional magnetic resonance imaging (fMRI) neurofeedback. Several studies have employed this method, two of which focused on the self-regulation of lower visual areas. Scharnowski, Hutton, Josephs, Weiskopf & Rees (2012) investigated whether perceptual enhancements would occur after neurofeedback training of ongoing spontaneous activity in retinotopic visual cortex. Participants were asked to detect the presence of a near-threshold visual stimulus during different blocks of up-regulation. Successful up-regulation resulted in improved detection performance only when the visual stimulus was presented in the visual field position corresponding to the retinotopic location of the region from which participants had received neurofeedback training. Shibata, Watanabe, Sasaki & Kawato (2011) investigated whether the successful up-regulation of primary and secondary visual cortex (V1/V2) areas could induce visual perceptual learning (VPL) without external stimulus presentation. VPL is a performance improvement on a visual task caused by repetitive training. Neurofeedback was provided from brain activation patterns corresponding to gabor patches of a specific orientation, but participants were unaware of what the feedback represented. Nevertheless, participants learned to match the, unknown, target brain activation pattern and showed an improved performance on an orientation discrimination task for that target orientation only. In both studies it can be ruled out that changes in brain activation were caused by the experimental manipulation and their findings suggest that perceptual enhancements were caused by heightened brain activation opposed to vice versa.

A study that explored the behavioural consequences of the self-regulation of higher visual areas targeted the fusiform face area (FFA) and the parahippocampal place area (PPA; Ekanayake et al., 2013). These areas are involved in the processing of faces and scenes respectively. The study investigated whether the up-regulation of one of these areas resulted in perceptual changes in a BR paradigm. After the neurofeedback training, the perception of the stimulus related to the target area remained unchanged.

However, a decrease in the duration and switch rate of the scene was found when participants had been up-regulating the FFA and vice versa. When participants were simultaneously engaged in the self-regulation and BR task, a further decrease in the duration and switch rate of the non-target stimulus was found. The latter perceptual changes were likely to be mediated by changes in attention as opposed to brain activation (Chong et al., 2005). Participants with the task to up-regulate for example the FFA were likely to attempt to focus on the face image and thereby bias the perception.

Weiskopf et al. (2004) presented participants with differential feedback of the PPA and supplementary motor area (SMA) and found that participants were successful in increasing PPA activation while decreasing SMA activation and vice versa. The study did not investigate any behavioural changes. An important advantage of differential feedback compared to single region feedback is the increased specificity by cancelling out for instance global drift and whole brain activation changes. In the current study, differential feedback from two higher visual areas, the FFA and the PPA, was used which increased task difficulty but allowed drawing more specific conclusions about the relationship between brain activation and visual perception. Importantly, both areas fulfil two essential requirements for successful neurofeedback training. First of all, these areas can be reliably localised as numerous studies have shown the consistent involvement of these areas in the processing of faces (Grill-Spector, Knouf, & Kanwisher, 2004; Kanwisher, McDermott, & Chun, 1997) and scenes respectively (Epstein, Harris, Stanley, & Kanwisher, 1999; Epstein & Kanwisher, 1998; Walther, Caddigan, Fei-Fei, & Beck, 2009). Second of all, it can be assumed that the activation in both areas can be self-regulated. Top-down mechanisms such as imagery have namely been found to activate these regions and additionally the possibility to up-regulate the PPA has already been demonstrated (O'Craven & Kanwisher, 2000; Weiskopf et al., 2004). Moreover, activation in both areas has not only been related to objective, but also subjective percept. The neural correlates of subjective perception have namely been found in higher visual processing areas (e.g. Lumer, Friston, & Rees, 1998; Rees, Kreiman, & Koch, 2002). Tong, Nakayama, Vaughan and Kanwisher (1998) for instance presented participants with a BR paradigm

involving a face and scene while being in the MRI scanner. Whenever participants indicated to be perceiving the face, the activity in the FFA increased while activation in the PPA decreased and vice versa. Unfortunately this study does not shed any light on whether the increase in FFA (or PPA) activity resulted in the face (or scene) being experienced as more dominant, or whether the face (or scene) was perceived as more dominant resulting in the FFA (or PPA) becoming more activated. Neurofeedback training circumvents this issue by transforming brain activation from the independent into the dependent variable and by examining what behavioural (or perceptual) changes occur as a consequence.

The current study explored the feasibility of PPA and FFA self-regulation and the potentially concomitant perceptual changes. It has been found that imagery can bias the subsequent perception of ambiguous stimuli towards the imagined stimulus (Pearson, Clifford, & Tong, 2008). It was therefore hypothesised that the simultaneous PPA up-regulation and FFA down-regulation would improve the reaction time of making judgements about scenes, but not faces, and would elongate the dominance of the scene, but not the face, in a BR paradigm. This study was of interest for two reasons. First of all, the outcome of this study aided the design of the control group in the neurofeedback and depression study that is described in Chapter 5. Any perceptual enhancements caused by PPA up-regulation could have a positive influence on depressive symptoms, thereby rendering the control group less powerful. Second of all, it allowed investigating the link between activation levels in visual brain areas and perception via top-down mechanisms in a direct fashion.

4.3 Methods

4.3.1 Participants

Seventeen participants were recruited via the Experimental Management System (EMS) of Cardiff University. All participants had normal vision or corrected-to-normal vision via contact lenses. The time slots advertised on the

EMS either corresponded to an MRI scanner booking or a mock scanner booking, so the slot a participant signed up for determined whether that person was assigned to the experimental (NF) or control (IM) group. Due to one participant in the NF group not experiencing any BR and due to technical issues with the response recording of another participant in the NF group, one more slot was advertised for the NF than IM group. Therefore, nine participants (5 female, 1 MRI naive, average age = 23.4 y) were assigned to the experimental group and eight participants (all female, 4 MRI naive, average age = 22.6 y) to the control group. All participants gave written informed consent at the beginning of the study. The study was approved by the Ethics Committee of the School of Psychology, Cardiff University. Participants were given the choice to either receive 11 course credits or £27.50 for their time and effort.

4.3.2 Materials

The strategies that participants could have come up with to up-regulate the PPA could either be imagery based or could involve constructing sentences related to scenes. Because the latter has been found to deactivate these areas, subjects were instructed to use imagery of scenes (Aziz-Zadeh et al., 2008). As it was unlikely that individuals without the ability of vivid imagery would be able to successfully execute any self-regulation, the Vividness of Visual Imagery Questionnaire (VVIQ; Marks, 1973) was used as a screening measure. Only participants with an average score of three or lower were included in the study (lower scores reflect more vivid imagery).

In order to investigate any relation between self-regulation ability and cognitive control, the Thought Control Questionnaire (TCQ; Wells & Davies, 1994) and the Thought Control Ability Questionnaire (TCAQ; Luciano, Algarabel, Tomás, & Martínez, 2005) were administered. These measures were also compared with a sample of depressed patients (see section 7.4.2) to validate Bandura's self-efficacy theory (see section 1.2.1).

Judgement task

The Judgement task was incorporated as a relatively implicit measure of perceptual change and to pick up any potential changes that were too short-lived to be picked up by the BR paradigm. The stimuli consisted of face images transparently superimposed on scene images. For the face images, nine neutral male and female faces were selected from the Radboud Faces Database (RaFD; Langner et al., 2010). All faces were cropped to a rectangular shape to eliminate all hair around the head. For the scene images, six images were selected from the Internet for each of the three subcategories landscapes, house interiors and house exteriors. Half of the house exterior images captured the complete front view of the house, the other half captured the front view partially. The 18 pictures in both categories were transformed into grey scale and each face image was paired with one scene image to create 18 picture pairs. The transparency settings required to perceive the two images that made up each picture pair with equal prominence, were measured for each participant individually. A staircase procedure in PsychoPy (Peirce, 2007) increased the transparency of the face image benchmarked against a fixed transparency of .5 for the scene image if the face was judged as less prominent. In turn it decreased the transparency when it was judged as more prominent. Transparency changes initially occurred in steps of .1, after two reversals this lowered to .05 and after another two reversals to .01. The staircase procedure finished after at least 15 responses and at least 4 reversals had occurred.

The Judgement task was composed of two conditions. In the Face Condition participants had to decide whether the face was male or female and had to make a button press accordingly. In the Scene Condition participants made a button press to indicate whether the scene represented an indoor or outdoor scene. The letters flanking the picture pair indicated whether participants had to judge the face or scene and were either an M (male) and F (female), or an I (indoor) and O (outdoor). Letter presentation side was counterbalanced across participants. Participants were asked to respond as fast and accurate as possible and reaction time (RT) and accuracy were recorded. All reaction times faster than 200 ms or slower than 3000 ms were classified as incorrect and were excluded from the

RT analysis. Button presses were recorded via an MRI compatible LumiTouch™ (Photon Control, Canada) response box. Participants were asked to maintain fixation on the fixation cross that was presented in the middle of each picture pair.

Binocular rivalry task

For the BR task a True3Di™ monitor (Redrover) and polarised glasses were used to present the images. The image of the scene, presented to the left eye, and the image of the face, presented to the right eye, were similar to the images used by Tong, Nakayama, Vaughan and Kanwisher (1998). Subjects indicated their perceptual alternations via two raised buttons on a keyboard. Participants were asked to keep their blinking rate constant and to not attempt to bias either image. Participants completed two blocks of BR before (Block 1 and 2) and after (Block 3 and 4) their scan and each block consisted of four trials that lasted 100 s each. All trials were separated by a 30 s rest period and both blocks were separated by a rest period of 110 s (Figure 4.1). This task was executed with the lights switched off. As the duration of any changes induced by the neurofeedback were expected to be short-lived, the analysis compared Block 2 and 3 to investigate any perceptual changes. The BR measures obtained were the number of button presses to indicate a predominance of face 'Face_hit' and scene 'Scene_hit', total predominance duration of face 'Face_total' and scene 'Scene_total' and rivalry rate 'BRrate'.

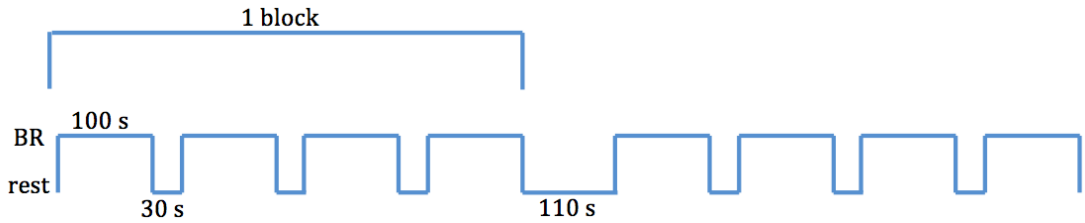

Figure 4.1. Design binocular rivalry task. BR = binocular rivalry.

Eye Tracking

The activation changes in the frontal eye fields (FEF) that are related to eye movement affect the activation in lower visual areas, which in turn can affect higher visual areas (Taylor, Nobre, & Rushworth, 2007). A combination of top-down and bottom-up mechanisms related to eye movement can thus lead to increased activation levels in the target area. Therefore, an MRI compatible eye tracking system (SMI iView X^{TM}, SensoMotoric Instruments) was used to record the pupil position of the right eye with a sampling rate of 50 Hz. The amount of eye movement was correlated with the self-regulation ability in the PPA. The distance between the origin and pupil position was calculated in MS Excel (MS Office 2011 for Mac OS X) for each sampling point in the self-regulation condition. The sum of the absolute differences between the distance of a sampling point and the next was then correlated with self-regulation performance in the PPA to investigate the relation between activation increments and eye movement. This distance measure did also pick up eye movements of equal size but in the opposite direction as pupil position was recorded in positive numerical coordinates. A drawback however is that any change in pupil position distance that is coincidentally equal in size but occurring over different distances along the x and y axes would not be picked up. As changes on the display presented during the self-regulation runs only occured in the y direction, it is highly unlikely that this drawback poses a problem in the current design. All behavioural and eye tracking data were analysed in SPSS 20 (SPSS Inc., Chicago, IL, USA).

Neurofeedback

The NF group received differential feedback from the FFA and PPA, which were identified via a functional localiser that consisted of images of faces, scenes and animals and lasted approximately 11 min. Twenty-four neutral faces were selected from the RaFD database. Twenty-four animals were selected from an animal database provided by Prof Paul Downing (Bangor University). The Internet was searched for six landscape pictures, six house interiors and twelve house exteriors to make up the scenes category. Stimulus blocks were presented in pseudo-randomised order, each block consisting of four images of

the same category presented for 1.5 s each. The stimuli used in the localiser were different from the stimuli used in the Judgement task.

The feedback provided to the NF group during the practice run was calculated and presented in the same way as during the self-regulation runs in the depression study (see section 2.1.3). Percent signal change (PSC) was calculated slightly different during the self-regulation runs, which were composed of three loops of a 36 s Self-regulation task, a 24 s Judgement task and a 20 s rest period (Figure 4.2). During the Self-regulation task participants were asked to increase the activation in the PPA as much as possible compared to the activation in the FFA. Participants in both groups were informed that they should imagine scenes while refraining from imagining faces in order to do so. Participants in the NF group were only presented with an increased number of red blocks on the thermometer dial if the activation levels in the PPA increased more than in the FFA. To realise this Turbo Brain-Voyager (TBV) outputted the activation values of the FFA and PPA separately, which PsychoPy used to calculate PSC for each region-of-interest (ROI) individually. It then calculated PSC_PPA – PSC_FFA in the same way as during the rest condition (opposed to the self-regulation condition) in the practice run. The reason for this was that no baseline condition was included at the start of the run to keep overall run duration within the limits imposed by the real-time setup. The shaping factor (SF; see section 2.1.3) was kept similar for all participants and was set at 10000.

4.3.3 Procedure

All participants took part in two separate sessions that were scheduled within a two-week time frame. Session one lasted 30 min in which the VVIQ, TCAQ and TCQ were administered. Additionally, participants thresholded all picture pairs of the Judgement task. Both groups were informed about the role of the FFA and PPA in the processing of, both real and imagined, faces and scenes. Session two lasted 135 min and started with the BR task. Participants in the NF group were then taken into the MRI scanner and participants in the control group to the mock scanner. Where appropriate recordings of an echo-planar

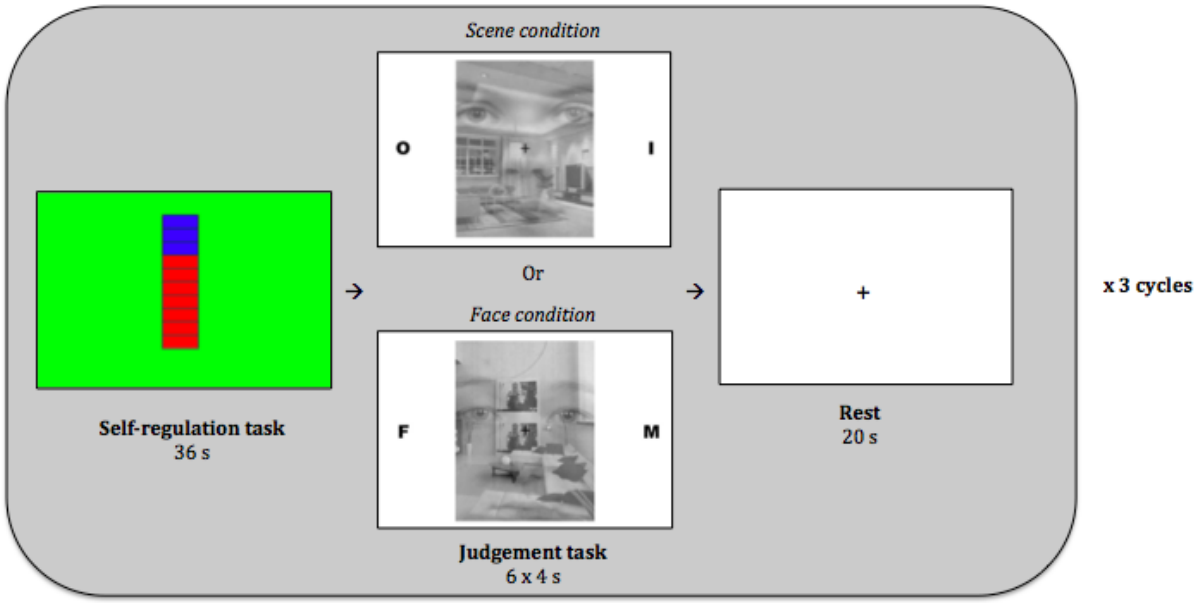

Figure 4.2. Design of each self-regulation run.

imaging (EPI) sequence were played back to participants in the mock scanner, who all wore earplugs. Respiratory rate, heart rate and pupil position of the right eye were recorded. Once set up in the scanner, participants completed a baseline rating of the Judgement task. The baseline rating was divided in three blocks and in each block each picture pair was shown, in randomised order, for 4 s in the face condition and 4 s in the scene condition. During the baseline rating task, a T1-weighted anatomical scan was obtained in the NF group and the recording of a fast spoiled gradient-recalled (FSPGR) sequence was played back to the IM group. Then the actual scan begun, starting with the localiser and followed by a practice run. While the NF group was presented with an updated thermometer screen that reflected activation levels in the PPA, the IM group watched a thermometer screen that was fixated halfway across the dial. Participants in the NF group were informed that due to the method via which the MRI scanner measures brain activation, it would take between 4-8 s before a change on the thermometer could be induced by their altered brain activation. After the practice run six self-regulation runs were conducted. During the Judgement task six picture pairs (of which three in the Face condition and three in the Scene condition, presented in randomised order) were presented for 4 s each. Each picture pair occurred once for each condition during the first two

runs, once during the middle two runs and once during the final two runs. During the rest period participants were presented with a fixation cross and instructed to count downwards from 99 in steps of three. Lastly, participants carried out the BR task once more. All participants were debriefed verbally and in writing.

4.3.4 Offline fMRI data analysis

BrainVoyager QX 2.3 (Brain Innovation, Maastricht, The Netherlands) was used for the offline imaging analysis. Standard fMRI pre-processing steps were carried out which were motion correction, temporal high pass filtering (2 sine/cosine pairs), spatial smoothing (6 mm FWHM Gaussian filter) and temporal smoothing (3 s FWHM Gaussian filter). All self-regulation runs were aligned to the first volume of the localiser run. Heart rate and respiratory rate measures were included as covariates in the general linear model (GLM). The *t*-statistic for the self-regulation predictor in the GLM of the FFA and PPA was extracted for each run as a measure of self-regulation performance.

4.4 Results

There was no significant difference in age between both groups ($p > .5$). A chi-square test was used to investigate any group differences for gender and MRI naivety. There was a significant association between *Group* and *Gender* (χ^2 [1] = 4.650, $p = .031$) but not between *Group* and *MRI naivety* (χ^2 [1] = 3.085, $p = .079$). It must be noted however that the expected count was less than 5 in 50 - 75% of the cells on both tests respectively, potentially rendering the chi-square statistic inaccurate.

4.4.1 Imaging results

All participants were able to carry out the Self-regulation task successfully, i.e. averaged over six runs all participants showed higher activation in the PPA than in the FFA (Figure 4.3). Some participants achieved this by up-regulating the

PPA more than up-regulating the FFA, others by up-regulating the PPA while down-regulating the FFA. The differential self-regulation performance, calculated by the *t*-statistic in the PPA minus that in the FFA, was significantly different from zero (one sample *t*-test, $t(8) = 4.670$, $p = .002$). In general, physically presented stimuli induced stronger activation increases in the PPA than imagined stimuli (Figure 4.4). It must be noted however that tasks of different lengths were compared here and that the activation value of the localiser is biased as the selection of the target area was based on this value.

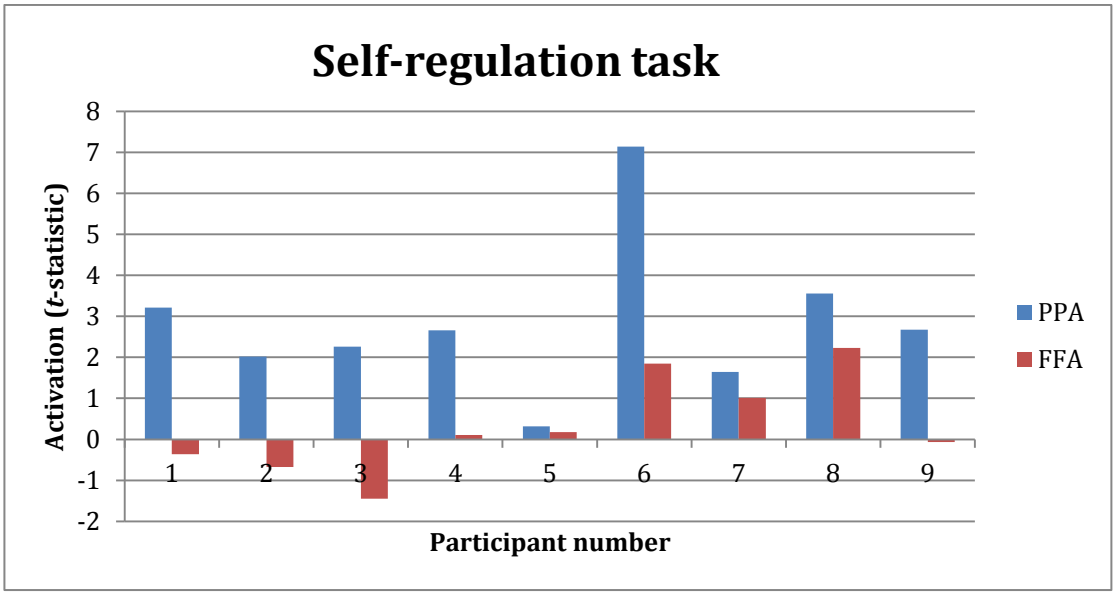

Figure 4.3. Neurofeedback performance per target area per participant represented by the *t*-statistic of the self-regulation predictor and averaged over all runs. All participants were able to obtain a higher activation level in the parahippocampal place area (PPA) than in the fusiform face area (FFA), as per instruction.

The size of PPA target areas was significantly larger than that of FFA target areas ($t(16) = 3.862$, $p = .001$; Table 4.1). This was a consequence of a smaller number of voxels being responsive to the face images than to the scene images during the localiser. It could be argued that the successful differential self-regulation of the PPA and FFA was mediated by differences in target size. The significant correlation between ROI size and self-regulation ability, defined as absolute *t*-statistic, seems to support this ($r = .505$, $p = .033$).

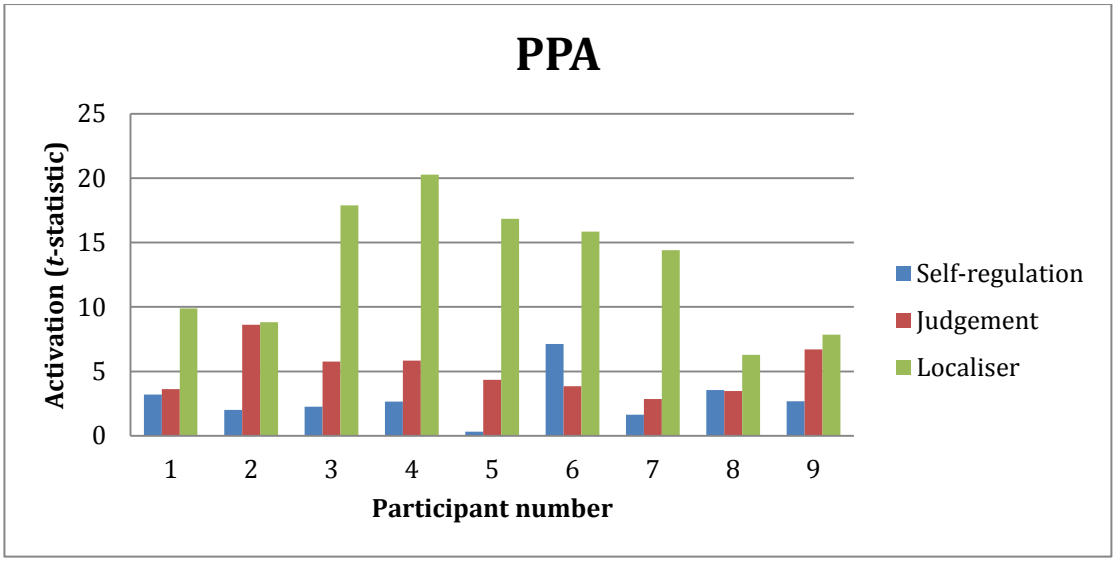

Figure 4.4. Activation levels in the parahippocampal place area (PPA) per task per participant, represented by the *t*-statistic of the self-regulation predictor and averaged over all runs. In almost all participants, real stimuli resulted in stronger activation than imagined stimuli.

	ROI details			
	PPA		FFA	
Participant	*Nr of voxels*	*TAL coordinates*	*Nr of voxels*	*TAL coordinates*
1	2945	25, -42, -15	2192	48, -59, -16
2	4245	23, -38, -13	940	35, -46, -21
3	3409	-24, -43, -13	3849	42, -62, -12
4	4481	-23, -52, -16	1362	42, -62, -19
5	1979	-22, -47, -9	1353	44, -65, -10
6	4000	-22, -45, -13	594	36, -47, -19
7	3447	-23, -47, -13	1827	42, -64, -14
8	2206	-25, -48, -11	1446	41, -62, -17
9	5429	-21, -55, -12	1819	-52, -44, -10

Table 4.1. Talairach coordinates of the selected target areas per participant. ROI = region-of-interest, PPA = parahippocampal place area, FFA = fusiform face area.

A previous functional imaging study adopting a motor imagery paradigm found that the larger the synaptic distance between an activated area and the V1, the larger the activation (Goebel, Khorram-Sefat, Muckli, Hacker, & Singer, 1998). To test if our data showed a similar pattern, five areas with varying synaptic distance from V1 were selected that were activated during both the presentation of scenes in the localiser run and during the imagery of scenes in the self-regulation runs (Table 4.2). Beta values of activation clusters centered over the peak voxel in the left and right hemisphere were extracted and averaged over both hemispheres. The activation level in the PPA was set as 1 and the activity in other areas was calculated as a ratio of PPA activation because the durations of the localiser and self-regulation condition were different (Figure 4.5). A roughly similar pattern to Goebel et al. (1998) was found, albeit less pronounced. The main reason for this is that in the current study participants did not view a blank screen but a changing thermometer while they were conducting the imagery, resulting in marked V1 activation during the Self-regulation task.

	TAL coordinates	
	Localiser run	*Neurofeedback runs*
V1	L: -10,-89,-9 R: 11,-89,-6	L: -12,-94,-8 R: 8,-95,-8
PPA	L: -26,-53,-13 R: 26,-50,-14	L: -27,-42,-11 R: 24,-38,-11
SPL	L: -29,-58,38 R: 25,-63,36	L: -23,-63,38 R: 26,-57,38
FEF	L: -39,-15,45 R: 40,-11,40	L: -42,-6,45 R: 41,-9,43
MFG	L: -38,9,26 R: 35,18,24	L: -47,16,28 R: 45,20,25

Table 4.2. Talairach coordinates of peak voxels in five areas with varying synaptic distance from V1. V1 = primary visual cortex, PPA = parahippocampal place area, SPL = superior parietal lobule, FEF = frontal eye field, MFG = middle frontal gyrus.

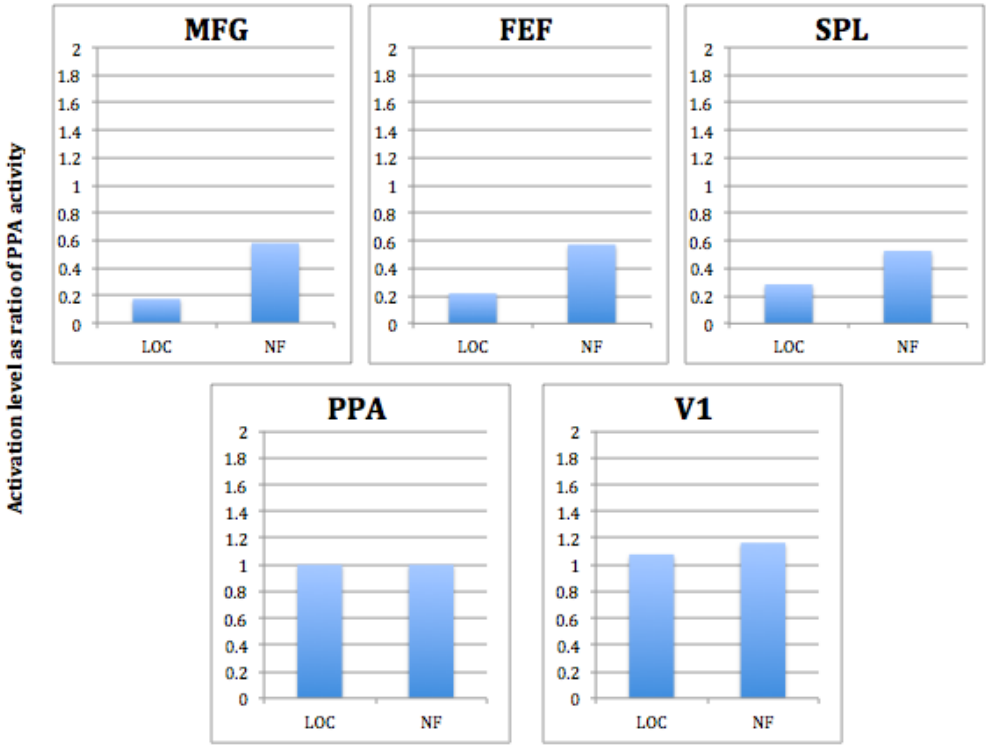

Figure 4.5. Activation patterns in five areas activated during both the localiser (LOC) run and neurofeedback (NF) run. Activation levels are denoted as a ratio of PPA activation. Areas with a larger synaptic distance from the primary visual cortex (V1) seem to be activated more during the neurofeedback than the localiser runs.

4.4.2 Behavioural results

Judgement task

There was no significant group difference at baseline in the Face Condition for RT (mean NF = 1.614 s; mean IM = 1.689 s, $t(14) = -.762$, $p > .4$) and accuracy (mean NF = 19.63 incorrect responses; mean IM = 19.13 incorrect responses, $t(14) = .251$, $p > .8$) nor in the Scene Condition for RT (mean NF = 1.350 s; mean IM = 1.376 s, $t(14) = -.226$, $p > .8$) and accuracy (mean NF = 1.50 incorrect responses; mean IM = 3.38 incorrect responses, $t(14) = -1.729$, $p > .1$). A two-way MANOVA with the factors *Group* (NF/IM) and *Time* (Baseline/Scan) was conducted with the dependent variables 'Faces_RT', 'Scenes_RT', 'Faces_accuracy' and 'Scenes_accuracy'. Normal distribution of the data was assumed as the Kolmogorov-Smirnov test tested non-significant

for all variables (all *p*s > .06). Although Box's test (F [30,2155.532] = 1.011, p = .450) was non-significant, a significant Levene's test of equality of error variance for the variable 'Scene_Accuracy' (p = .031) suggests unequal variance between both groups. Transformation of this variable did not resolve the unequal variance. The MANOVA did not yield a significant interaction (F [4,25] = .296, p = .878) but returned a significant effect of *Group* (F [4,25] = 2.942, p = .04) and a marginally significant effect of *Time* (F [4,25] = 2.566, p = .063). The main effect of *Group* was caused by higher 'Scene_accuracy' scores in the NF than IM group at both time points (F [1,28] = 6.703, p = .015; Figure 4.6). To account for the unequal variance between both groups on this variable, a Brown-Forsythe test was used which confirmed a significant difference between both groups on the variable 'Scene_Accuracy' (F [1,23.479] = 6.680, p = .016).

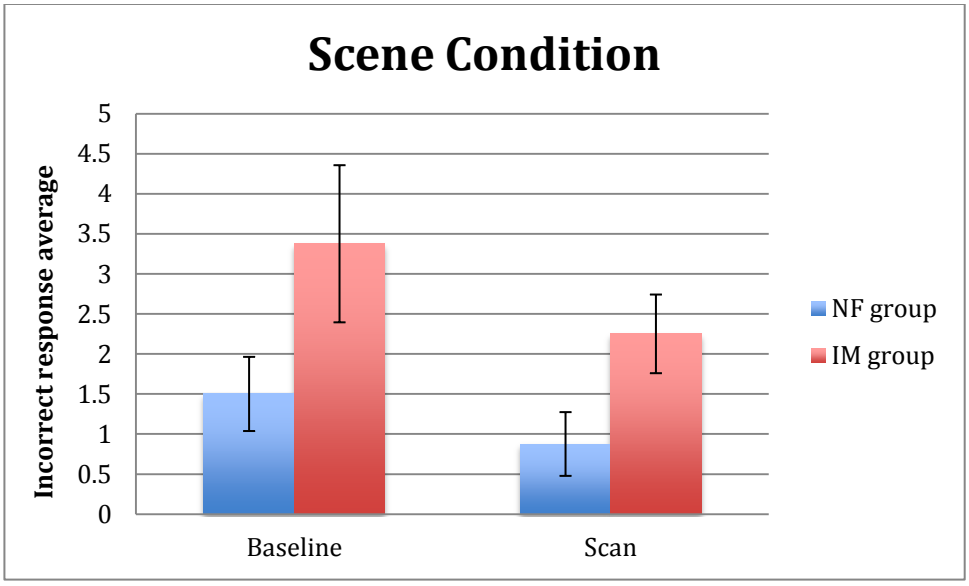

Figure 4.6. Accuracy on the Scene Condition of the Judgement task. Both at Baseline and at Scan, participants in the NF group made less incorrect responses.

To assess any potential non-specific effects caused by gender, a univariate ANOVA was run within the NF group with the fixed factor *Gender* and the dependent variable 'Scene_Accuracy' collapsed over both time points. The effect of *Gender* was found to be non-significant (p = .271), but it must be noted that this outcome may be due to the small sample size.

The marginally significant effect of *Time* was driven by a significant improvement on the variables 'Faces_RT' (F [1,28] = 6.258, p = .018; Figure 4.7) and 'Scenes_RT' (F [1,28] = 5.311, p = .029; Figure 4.8) during Scan compared to Baseline.

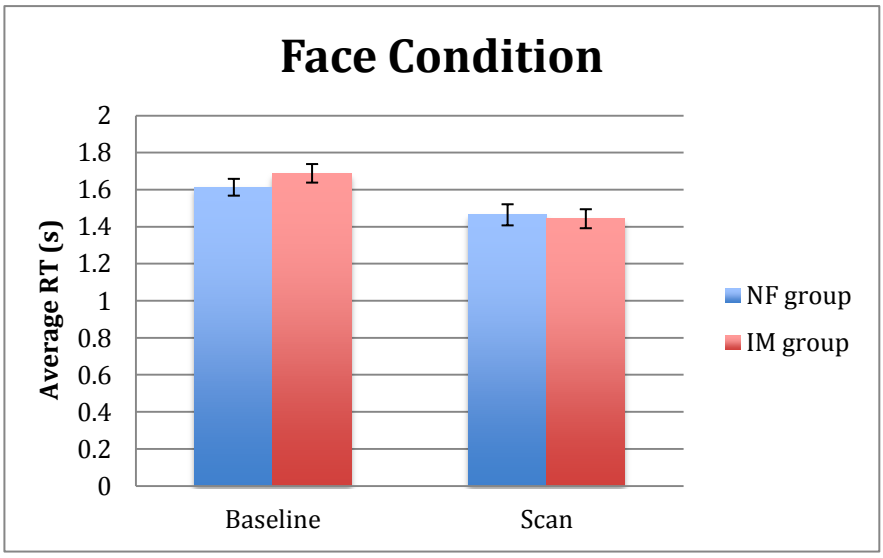

Figure 4.7. Reaction Time (RT) on the Face Condition of the Judgement task. Participants in both groups responded faster during Scan compared to Baseline.

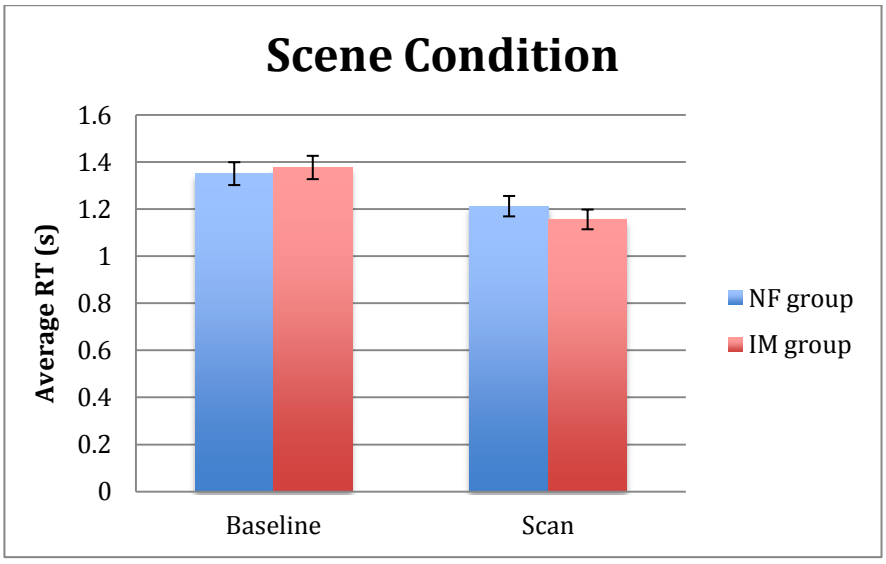

Figure 4.8. Reaction time (RT) on the Scene Condition of the Judgement task. Participants in both groups responded faster during Scan compared to baseline.

Binocular rivalry task

There were no significant differences between both groups at baseline for any of the binocular rivalry measures (all *p*s > .1). A two-way MANOVA with the

factors *Group* (NF/IM) and *Time* (Block2/Block3) was conducted with the dependent variables ‘‘Face_hit’, ‘Scene_hit’, ‘Face_total’, ‘Scene_total’, and ‘BRrate’. Kolmogorov-Smirnov tests indicated a non-normal distribution of the variable ‘Scene_total’ in Block2 in the NF group (p = .005) and Block3 in the IM group (p = .031), as well as of “Face_total’ in Block3 in the NF group (p = .024). Various transformations of the variables ‘Scene_total’ and ‘Face_total’ did not improve their distribution. Because Box’s M test indicated heterogeneous variance-covariance matrices as well (F [45,1940.629] = 104.136, p = .014), the outcome of the MANOVA must be treated with caution. However, equality of variances between groups could be assumed for all variables with all Levene’s tests being non-significant (all ps > .2). The MANOVA did not yield a significant interaction between *Group* and *Time* (*Pillai’s F* [5,24] = .743, p = .599). A main effect was found for *Group* (*Pillai’s F* [5,24] = 3.828, p = .011) but not for *Time* (*Pillai’s F* = [5,24] = .566, p = .725). Post-hoc tests showed that the significant effect of *Group* was mediated by group differences on the variables ‘Scene_total’ (F [1,28] = 12.770, p = .001; Figure 4.9) and ‘Face_total’ (F [1,28] = 11.340, p = .002; Figure 4.10). Participants in the NF group perceived the scene image for a smaller overall amount of time than participants in the IM group while the opposite was the case for the face image.

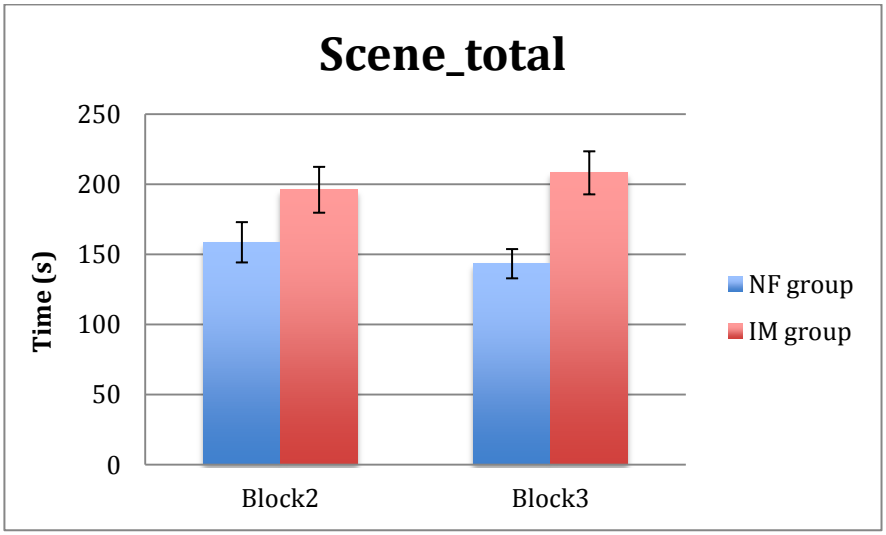

Figure 4.9. Predominance of the scene image on the Binocular rivalry task. Participants in the NF group perceived the scene for a shorter overall duration than participants in the IM group.

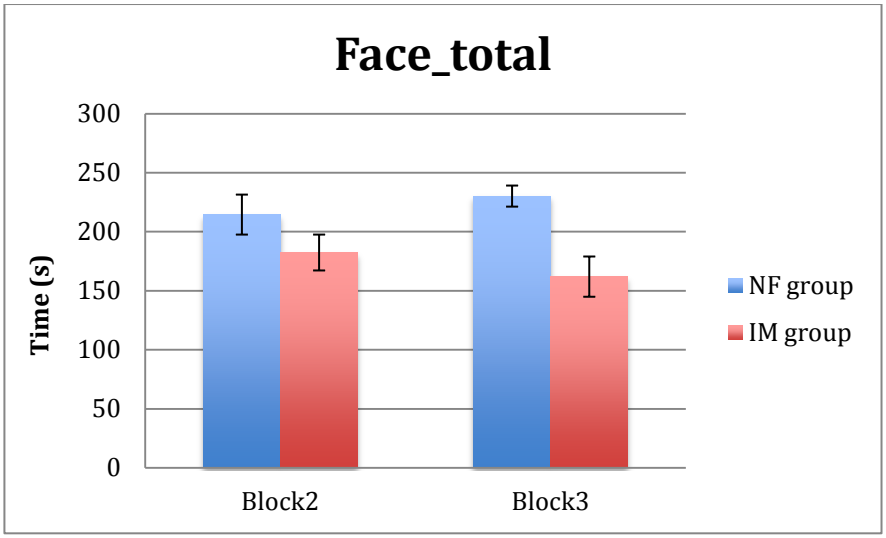

Figure 4.10. Predominance of the face image on the Binocular rivalry task. Participants in the NF group perceived the face for a longer overall duration than participants in the IM group.

4.4.3 Eye tracking

In five participants the volume triggers had not been recorded in the eye tracking data output file due to Matlab (Mathworks Inc) license issues or USB driver problems common in Windows 7. For the remaining four participants, a non-significant correlation was found between total eye movement and self-regulation ability in the PPA (r = .093, p = .690). The increase in activation in the PPA during the Self-regulation task compared to Rest was thus expected to arise due to mental imagery opposed to eye movement.

4.4.4. Psychometrics

There was no significant correlation between self-regulation ability on the one hand and TCQ or TCAQ on the other (all ps > .6).

4.5 Discussion

This study showed that it is possible to exercise control over the activity in visual processing areas via fMRI-based neurofeedback training. Although previous studies have found a similar result, these studies did not employ

differential feedback of two visual areas nor did they conduct eye tracking. The findings of the current study suggest that it is unlikely that eye movement mediated the successful self-regulation. The difference in absolute self-regulation ability between the PPA and FFA could have been the result of ROI size differences. However, one of the few neurofeedback studies that trained participants to down-regulate as well as up-regulate the target area, has shown that participants experience down-regulation as more difficult than up-regulation (Veit et al., 2012). The Self-regulation task in the current study can be expected to be even more difficult as participants had to perform a dual task given the distinct target areas involved. In coherence with the idea that imagery can be regarded as a weaker form of actual perception, the PPA activation during imagery was lower compared to actual stimuli presentation (Kosslyn, 1994).

It was hypothesised that the NF group would show larger perceptual changes after mental imagery combined with neurofeedback, than the IM group after mental imagery alone. The results of the Judgement task however suggest that there is no additional effect of neurofeedback training. It was found that the NF group, compared to the IM group, showed a significantly higher overall accuracy at judging the scene images. The non-significant *Group* x *Time* interaction may be explained by a ceiling effect as the low number of incorrect responses in the Scene Condition left little room for improvement. In addition, the results show that participants became faster in judging faces and scenes when comparing Scan to Baseline, but this improvement was comparable in both groups. Because this improvement was found for both faces and scenes it is likely that the underlying cause is VPL opposed to a behavioural change induced by mental imagery or, in case of the NF group, altered brain activation.

The findings of the BR task suggest that overall the participants in the NF group perceived the face as more preeminent than the scene and participants in the IM group experienced the scene as more predominant. As the most dominant percept in the NF group did not change over time, it seems that neurofeedback training of the PPA and FFA had no effect on bistable perception. Several factors may have contributed to this outcome. First of all,

even though the PPA and FFA are involved in the processing of scenes and faces, they might not be involved in maintaining a dominant percept or inducing a perceptual transition. Indeed, studies using TMS or caloric stimulation to interfere with BR perception have found that targeting the parietal cortex affected the temporal dynamics of BR (Carmel et al., 2010; Miller et al., 2000). Related to this Tong et al. (1998) found that the activation in the FFA and PPA reflected the dominant percept on a BR task. They therefore suggested that rivalry is resolved at a lower level of visual processing. The findings of the current study imply that any top-down influence from the PPA or FFA did not affect this lower stage. Another explanation for the current outcome might be that the BR paradigm employed may not have been optimal to detect any neurofeedback-induced perceptual changes. Any changes can namely be expected to be short-lived because of a) the relatively short overall duration of the neurofeedback training. While the current study included 12 min of neurofeedback during the self-regulation runs and three min during the practice run, Scharnowski et al. (2012) presented feedback for a total of 49 min. Shibata et al. (2011) conducted either five or ten sessions so participants executed either a total of 81 or 162 minutes of self-regulation. b) Participants were asked to bring activation levels back to baseline during the Rest component of the self-regulation run. Scharnowski et al. (2012) only found changes in perception when the perceptual sensitivity task was carried out while participants were exercising control over their visual cortex activation. This finding highlights how short behavioural changes induced by neurofeedback may last. A BR setup compatible with the MRI environment would allow the simultaneous occurrence of BR and self-regulation and may be more sensitive to pick up any perceptual changes caused by neurofeedback.

Another drawback of the current study is that it is unknown whether the participants in the control group managed to differentially activate their PPA and FFA because they performed the self-regulation runs in the mock scanner. Related to this some may argue that because some participants were aware of not being in a real MRI scanner, they were less motivated to perform to the best of their ability. This is unlikely to be the case because the RT and accuracy in both groups were highly comparable. In addition, the eye tracking data were

monitored during the experiment and confirmed that participants attended to the tasks.

A replication of the current study with more sessions and a more suitable BR setup is required to confirm the findings of this pilot. In addition, a larger sample size will have to be used to render the outcome of the statistical tests more reliable. A more difficult Scene Condition of the Judgement task could be incorporated or the task could be replaced by a different type. A detection task could for instance be incorporated in which participants have to indicate whether stimuli presented at a low detection threshold represent a face or scene. The study would also benefit from the inclusion of a scanned control group. Alternatively, the addition of control groups that investigate the sole effect of stimulus presentation or imagery on BR might be able to shed light on the mechanisms underlying the unexpected BR findings. It would also be interesting to swap the target and control ROI, although pilots of the current study have shown that participants find it harder to up-regulate the FFA while down-regulating the PPA than vice versa.

Since the results of the current study do not suggest that PPA up-regulation results in perceptual enhancements, neurofeedback from the PPA was selected as the control in the depression study described in Chapter 5. As the involvement of differential feedback opposed to feedback from a single area increases the difficulty of the neurofeedback task, it was chosen to provide the control group in the depression study with feedback solely related to PPA activation.

Chapter 5 - Physiological self-regulation via neurofeedback training in depression

5.1 Abstract

Depression is associated with aberrant activation patterns in a variety of brain areas, such as hypoactivation in emotion regulation areas. Neurofeedback training has the potential to target the neurobiological substrate of depression in a non-invasive, individually tailored way. In this study, sixteen moderately to severely depressed patients took part in a course of neurofeedback training consisting of four weekly sessions and a final session after a one-month break. During the third session patients did not receive any feedback to assess any transfer effects. Patients were randomly assigned to a group receiving real-time functional magnetic resonance imaging (fMRI) neurofeedback from an area involved in processing positive emotions (EMO group) or from the parahippocampal place area (PPA) which is involved in scene processing (PPA group). To localise the individualised target areas, patients in the EMO group were presented with positive, negative and neutral pictures of the International Affective Picture System (IAPS) and patients in the PPA group with pictures of scenes, faces and animals. Commonly selected target areas in the EMO group included the ventrolateral prefrontal cortex (VLPFC), dorsolateral prefrontal cortex (DLPFC) and insula. Depending on the assigned group, patients were asked to up-regulate the activation in their target area by positive emotion imagery or calming scene imagery. All patients learned to exercise voluntarily control over their target area, with patients in the EMO group showing better self-regulation performance during the last two sessions compared to the first two and PPA group patients showing the opposite pattern. Self-regulation ability was not confounded by respiratory rate or heart rate.

5.2 Introduction

Chapter 3 discussed the underlying rationale of applying neurofeedback training as a treatment tool for depression. One element of this rationale is the potential of neurofeedback to target positive emotion processing areas. The current chapter serves to validate the feasibility of training depressed patients with neurofeedback to achieve this. Although the findings of the pilot study, published in PLoS One (Linden et al., 2012) and described in section 2.3, already suggested the feasibility of this approach, the current study incorporated some adjustments. First of all, a fifth neurofeedback session was added a month after the fourth in order to test the durability of acquired physiological self-regulation ability without continuous training. This is of interest if neurofeedback were to become an add-on treatment for depression. In addition, the third neurofeedback session was replaced by a session without feedback to assess any transfer effects. This session served to estimate the minimum amount of neurofeedback training required before patients are able to exercise voluntary control over their brain activity in the absence of feedback. Moreover, participants were asked to practise the self-regulation strategies at home while awaiting their next session to maximise impact and to ensure patients arrived optimally prepared for their limited time in the scanner.

The current study also differed from the pilot study with respect to other important aspects, such as the design of the control group. A drawback of the control group in the pilot study was that it did not undergo the same intervention setup. While the patients in the experimental group received neurofeedback training in the magnetic resonance imaging (MRI) scanner, the control group executed a comparable imagery task without feedback in front of a computer. Therefore, the absence of an improvement in depressive symptoms in the control group could potentially be attributed to 1) the absence of the high tech environment provided by the MRI scanner, which may have influenced the patients' perception of how influential the treatment was going to be. 2) A sense of being allocated to the control group, which may have reduced the amount of effort put in the task. 3) A lack of receiving feedback which could have had a

positive influence on mood otherwise. In order to be able to rule out these factors, the control group in the current study received neurofeedback training in the MRI scanner as well, albeit from an area relatively unrelated to emotion processing. The overall amount of positive, hence potentially rewarding, feedback was kept similar between both groups by heightening or lowering the feedback sensitivity. Unlike the sequential group allocation that had been required in the pilot study to provide the control group with appropriate instructions for the imagery task, patients were randomly allocated to one of two groups. An adaptive randomisation program matched both groups for gender, medication and a variety of other factors (see section 5.3.1). The experimental group (EMO group) received feedback from emotion areas such as the insula and the control group (PPA group) from the parahippocampal place area (PPA), an area involved in processing scenes. In contrast to the pilot study (see section 2.3), the main dependent variable was assessed by raters blinded to group assignment. As different protocols were required for neurofeedback target localisation and selection in both groups, the experimental procedure did not allow the experimenter to be blinded to group assignment too. Patients were informed that the trial investigated two potential interventions that were both expected to have a positive effect on depression. This minimalised any bias of frustration which otherwise can result in larger improvements in the EMO group, thereby making the selected control even more stringent.

In principle, any area not involved in the processing of emotions would qualify as a control feedback region but the availability of such areas is limited. Many areas across the brain have been linked to emotion processing, putatively including the PPA. Aminoff, Kveraga, & Bar (2013) proposed that the PPA facilitates emotion understanding by merging emotion and contextual processing. Although this does not rule out limited involvement of emotion areas during neurofeedback training in the control group, a PPA control area offers a few advantages. A previous study (Weiskopf et al., 2004) and the findings presented in Chapter 4 have shown the feasibility of training (healthy) participants to self-regulate this area via neurofeedback. Second of all, this area can be described to patients as involved in the processing of calming scenery,

thereby making it a credible target area in a mood disorder study. Motor regions do not suffice as control area given the relation between depression and motor retardation (Fleminger, 1991).

This adapted control group design allows investigating whether any improvements in depression are specifically related to feedback from areas involved in emotion processing or not. As the overarching clinical trial is still in progress, this assessment cannot be presented in this thesis. Therefore, the current chapter focuses on presenting the physiological self-regulation performance findings.

5.3 Methods

5.3.1 Participants

Eighteen patients suffering from moderate or severe unipolar depression were recruited via GP surgeries and Community Mental Health Teams (CMHTs) within Cardiff & Vale University Health Board and via the National Centre of Mental Health (NCMH, an organisation supporting and undertaking mental health research in Wales). This sample is a subset, made up of the first recruits, of a currently still ongoing clinical trial (NCT01544205). Patients were only included if they had been taking stable anti-depressant medication for at least three months, were not receiving any other treatment for their depression other than medication, showed no bipolar or psychotic symptoms and met MRI safety criteria. Current substance dependence/abuse and eating disorders were ruled out in all patients. Two patients dropped out of the study, one patient because of claustrophobia experienced in the MRI scanner and one due to work-related issues. This resulted in a sample of sixteen patients, eight in each group. Patients were randomly assigned to neurofeedback training of a positive emotion processing area (EMO group) or a scene processing region (PPA group) via an adaptive randomisation procedure. This procedure was implemented by the South East Wales Trials Unit (SEWTU) of Cardiff University and matched both groups for age, gender, duration of illness,

medication type and depression severity at baseline. The study was approved by the South East Wales Research Ethics Committee. All patients signed a consent form before taking part in the study and were paid £10 per hour to compensate for their time and effort.

5.3.2 Materials

To practise the self-regulation at home, patients were provided with a CD that contained the (stationary) feedback screens presented during the neurofeedback runs. Patients recorded the frequency and duration of the practise sessions in a diary. This diary also contained pre-printed questions about the neurofeedback experience. The data from the patient diaries will not be presented in this thesis.

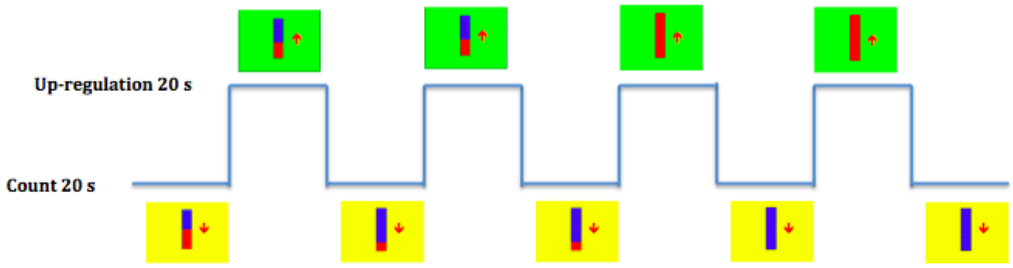

Figure 5.1. Design of a neurofeedback training run. A yellow background screen indicated that a patient had to count backwards, a green background that a patient had to attempt to increase the activation in the target area as much as possible via mental imagery. During each session, six neurofeedback runs were conducted.

5.3.3 Procedure

All patients came in for a screening session to confirm eligibility to take part in the study. Patients then took part in four sessions that were separated by one week. After a one-month break patients returned for a final neurofeedback session. In each session participants were first presented with a localiser of approximately ten minutes in order to identify the target area for the neurfeedback training. The EMO group was presented with positive, negative and neutral pictures from the International Affective Picture System (IAPS; (Lang et al., 1997) to identify an area responsive to positive emotions. IAPS pictures have been found to be suitable for depressed patients (Ritchey, Dolcos, Eddington, Strauman, & Cabeza, 2011). An area responsive to positive emotions was selected as the target area. This approach is justified by the

findings presented in Chapter 8, which show that distinct neural correlates underlie different types of valence in depression. The PPA group was presented with the same localiser as described in section 4.3.2 that consisted of pictures of faces, scenes and animals to identify the PPA.

Participants were then presented with the neurofeedback training task. Four up-regulation blocks of 20 s were flanked by 20 s blocks of counting backwards (Figure 5.1; see section 2.1.3). During the neurofeedback runs patients received feedback from their target area in the format of a thermometer display. The higher the activity in the target area, the more red blocks would appear on the thermometer dial. The task of patients was, depending on group assignment, to use the imagery of either positive emotions or relaxing scenes to increase the activation of their target area as much as possible. Because depression has been associated with cognitive impairments and down-regulation has been associated with a higher cognitive load compared to up-regulation (Veit et al., 2012), the latter was chosen as the set task. All patients were informed that due to the way the MRI scanner measures brain activation, it would take between 4-8 s before a change on the thermometer could be induced by their altered brain activation. Patients were therefore advised to stick to one particular strategy during each up-regulation block. During the Count blocks participants were asked to count backwards from 99 in steps of three. In each session patients completed six runs of the neurofeedback training task.

Heart rate and respiratory rate were measured during each session and a T1-weighted anatomical scan was obtained during the first. The third session was slightly different to the other sessions as patients were presented with a static thermometer opposed to real-time feedback displays. During this transfer session patients had to rely on previously successful strategies to achieve up-regulation of the target area. All patients were verbally debriefed after a follow-up assessment, which took place one month after the final neurofeedback scan.

5.3.4 Offline fMRI data analysis

Offline imaging analysis was conducted in BrainVoyager QX 2.3 (Brain Innovation, Maastricht, The Netherlands). The fMRI data were motion corrected via trilinear interpolation, temporal high pass filtered (2 sine/cosine pairs) and spatially (6 mm FWHM Gaussian filter) and temporally (3 s FWHM Gaussian filter) smoothed. All self-regulation runs were aligned to the first volume of the localiser run and transformed into Talairach space (Talairach & Tournoux, 1988). Heart and respiratory rate measures were included as covariates in the general linear model (GLM). The *t*-statistic for the self-regulation predictor in the GLM of the target area was extracted for each run. The data were then analysed in SPSS 20 (SPSS Inc., Chicago, IL, USA) using a repeated measures ANOVA.

5.4 Results

A variety of brain areas involved in emotion processing was selected in the EMO group, including the anterior insula and ventrolateral prefrontal cortex (VLPFC; Table 5.1). The PPA was successfully localised in all patients in the PPA group (Table 5.2). The self-regulation ability during the up-regulation condition was compared to the Count condition and any differences per session and group were assessed.

While patients managed to significantly up-regulate their target areas during the neurofeedback sessions ($t(15) = 2.239$, $p = .041$), this was not the case during the transfer session ($t(15) = .758$, $p = .460$). There was no difference in physiological self-regulation ability between both groups during the neurofeedback sessions ($t(14) = -.637$, $p = .534$) and the transfer session ($t(14) = .291$, $p = .775$). Also the size of the selected target areas was comparable in both groups ($t(14) = -1.693$, $p = .113$). A few of the strategies that patients reported to be successful are listed in Table 5.3.

	EMO			
Patient	*Session*	*Nr of voxels*	*Coordinates in TAL*	*Area*
1	*1*	249	-16,-9,-6	L amygdala
	2	674	40,23,10	R ant insula
	3	953	42,27,10	R ant insula/VLPFC
	4	812	48,32,11	R ant insula/VLPFC
	5	400	47,29,12	R VLPFC
2	*1*	484	43,29,12	R VLPFC
	2	526	41,26,12	R VLPFC
	3	791	38,23,13	R insula
	4	144	26,34,-6	R VLPFC
	5	201	24,35,-2	R VLPFC
3	*1*	479	41,16,-11	R VLPFC
	2	470	45,31,17	R VLPFC/DLPFC
	3	304	44,16,5	R insula
	4	1374	43,32,17	R VLPFC
	5	687	46,33,25	R VLPFC
4	*1*	13883	12,2,6	Bil putamen/insula
	2	2216	39,15,10	R ant insula
	3	2141	-35,21,5	L ant insula
	4	1636	-46,8,19	L ant insula
	5	952 3489	37,14,22 -36, 8, 12	R insula/VLPFC 2: L insula
5	*1*	1496	-6,21,11	Bil VLPFC
	2	1239	46,22,26	R insula
	3	1111	-44,36,15	L VLPFC
	4	510	33,20,14	R ant insula/VLPFC
	5	892	1,-12,-13	Bil amygdala
6	*1*	517 4820	-20,-2,-11 -36, 14, 4	L amygdala 2: L insula/caudate nucleus
	2	331 387	-21,-26,-7 23,11,5	L parahippocampal gyrus 3: R ventral striatum
	3	351	39,16,30	R DLPFC
	4	1857 2456	33,0,34 33,6,31	Bil DLPFC 3: Bil DLPFC + ant insula
	5	2903	41,8,34	R DLPFC
7	*1*	799	22,57,-3	R OFC
	2	4342	-41,1,32	L DLPFC
	3	1401	48,-2,42	R DLPFC
	4	1998	-40,4,29	L DLPFC
	5	2106	49,-2,37	R DLPFC
8	*1*	5586	37,15,23	R IFS
	2	1128 3715	0,1,8 -34,4,10	striatum 2: L VLPFC/ins
	3	4023	37,7,26	R VLPFC/DLPFC
	4	3890	39,16,20	R VLPFC
	5	4506 1516	37,18,21 38,12,12	R VLPFC/DLPFC 2: R VLPFC

Table 5.1. Details of the target areas selected in the EMO group. Multiple target areas are listed for session in which the target area was adjusted. The number preceding the hemisphere indication shows from which run on the change was effective. Coordinates are given in Talairach space. L = left, R = right, bil = bilateral, ant = anterior, VLPFC = ventrolateral prefrontal cortex, DLPFC = dorsolateral prefrontal cortex, OFC = orbitofrontal cortex, IFS = inferior frontal sulcus.

	PPA			
Patient	*Session*	*Nr of voxels*	*Coordinates in TAL*	*Side*
1	*1*	2023	25,-41,-12	R
	2	1793	21,-56,-13	R
	3	694	25,-45,-9	R
	4	3215	26,-43,-6	R
	5	816	25,-45,-10	R
2	*1*	1378	-1,-44,-13	Bil
	2	1333	-24,-38,-16	L
	3	1197	-22,-39,-13	L
	4	2818	26,-48,-12	R
	5	1137	-22,-51,-12	L
3	*1*	3606	2,-42,-8	Bil
	2	5187	1,-46,-7	Bil
	3	924	17,-57,8	R
	4	2082	-23,-42,-8	L
	5	9353	2,-43,-7	Bil
4	*1*	1872	28,-43,-13	R
	2	5149	0,-41,-11	Bil
	3	2040	-25,-42,-8	L
	4	1701	15,-41,-8	Bil
	5	3103	24,-40,-11	R
5	*1*	2517	-11,-47,-13	Bil
	2	2442	0,-49,-9	Bil
	3	2113	-24,-47,-14	L
	4	3215	24,-46,-11	R
	5	2638	-27,-49,-10	L
6	*1*	3759	-9,-46,-8	Bil
	2	3766 1333	31,-50,-12 -2,-44,-9	R 3: Bil
	3	5565	-1,-48,-8	Bil
	4	4075 461	7,-46,-11 27,-35,-16	Bil 3: R
	5	2060	-32,-45,-10	L
7	*1*	4448	1,-49,-12	Bil
	2	3017	-23,-47,-16	L
	3	3241	4,-48,-15	Bil
	4	2897	26,-47,-12	R
	5	3081	26,-48,-10	R
8	*1*	1116	21,-53,-16	R
	2	2063	-25,-50,-8	L
	3	3130	-20,-55,-8	L
	4	3934	-25,-48,-13	L
	5	4233	-23,-53,-9	L

Table 5.2. Details of the target areas selected in the PPA group. Multiple target areas are listed for session in which the target area was adjusted. The number preceding the hemisphere indication shows from which run on the change became effective. L = left, R = right, bil = bilateral.

Group	Patient	Reported successful strategies
EMO	**1**	Visualising sunny scenes Thinking of food and drinks Non-vocalised singing
	2	Thinking of her cats
	3	Thinking of wedding day Imagining a slide show of pictures of happy moments
	4	Thinking about her (laughing) daughter Thinking of house where grown up
	5	Thinking of (younger) family members Thinking of horse riding on the beach
	6	Thinking of her children
	7	Imagining powerful positive emotions in future or recent past
	8	Reliving holiday
PPA	**1**	Thinking of moving images such as motorbikes
	2	Imagining the localiser pictures of houses Imagining driving home with sea views
	3	Scanning the rooms in houses Thinking of a field with poppies
	4	Thinking of a beach Thinking of a wide field with a tree
	5	Imagining floating on the sea
	6	Imagining "being in" an image of a wooden house
	7	Thinking of own house Imagining lying in a field with blue bells
	8	Thinking of beaches

Table 5.3. Strategies employed by patients to up-regulate their target area.

To check that the online adjustment of the shaping factor SF had not affected the presented reward rate differently in both groups, an independent samples *t*-test was calculated. Reward rate was defined as the percentage of red blocks on the thermometer dial obtained out of the overall amount of red blocks "available" during the up-regulation. The average reward rate in the EMO group was 29% and in the PPA group 24%. No significant difference was found between the average reward rate that patients in both groups had received ($t(14) = 1.755$, $p = .101$).

A repeated measures ANOVA with the dependent variable 'Up-regulation ability' and the factors *Session* (4 levels) and *Group* (EMO/PPA) was computed. Kolmogorov-Smirnov tests indicated that the data were roughly normally distributed (all *p*s > .05). The data showed no violation of homogeneity of variance as all Levene's tests were non-significant (all *p*s > .5) nor of sphericity as Mauchly's test was not significant ($\chi^2(5) = 3.539$, $p = .618$). A marginally significant interaction between *Session* and *Group* was found

(F[3,12] = 3.153, p = .065). This resulted from a better up-regulation performance in the PPA group during all sessions apart from during the fourth (Figure 5.2). It thus seems that without training, or with relatively little training, it is easier to up-regulate the PPA compared to an emotion area. At the same time, it seems that it becomes harder to retain this increase in PPA activation after the first session, with the exception of the final session.

Figure 5.2. Up-regulation ability per group, per session. A marginally significant interaction was found between Group and Session (p = .065; transfer session 3 not included).

5.5 Discussion

The current chapter investigated whether patients suffering from depression were able to voluntarily increase the activation in emotion processing areas (experimental EMO group) or in a scene processing region (control PPA group). We found that patients in both groups were able to significantly up-regulate their target area. Already during the first session patients in the PPA group showed relatively high physiological self-regulation abilities, yet these did not improve any further over time. It seemed that patients performed relatively better when the up-regulation task had not been executed recently, such as during the first and last neurofeedback session. Relatively long term

habituation effects might underlie this observation. In contrast, the up-regulation of emotion processing areas seemed more difficult without any practise. Moreover, once successful up-regulation had been achieved in the EMO group, it seemed that continued training was required to maintain this ability. Booster sessions might thus be necessary for keeping patients' self-regulation ability of emotion networks at optimal performance. As patients did not succeed in up-regulating their target area during the transfer session, it seemed that after two training sessions patients still required feedback to execute the up-regulation task properly. Any booster sessions would thus have to be scheduled after an initial training consisting of more than two neurofeedback sessions.

Since there are no objective measures of what constitutes a positive mood or a non-depressed state of being, it was of especial importance for the currently ongoing clinical trial that any changes in depression in the experimental group were benchmarked against those in an apt control group. The findings in the control group of the pilot study suggested that the mere repetition of positive emotion imagery did not improve depression severity (Linden et al., 2012). The design of that study could however not rule out that clinical improvement in the experimental group was due to the specialist MRI environment or rewarding feedback. Therefore, the current control group also received neurofeedback training. Given the nature of the current sample, we opted for accurate feedback to minimise distress that could have been caused by a perceived inability to perform the task. We therefore selected a control area that was relatively unrelated to depression and emotion regulation.

A disadvantage of the current control group is that it cannot establish the importance of self-induced opposed to externally induced activation increases. Therefore it cannot validate Bandura's self-efficacy theory. Sulzer, Haller, et al. (2013) recently stressed the importance of control conditions that compare outcomes resulting from neurofeedback training with the best-known alternative method to excite the region-of-interest. To some extent, transcranial magnetic stimulation (TMS) could shed more light on the importance of playing an active role in establishing heightened brain activity. It must be noted

however that TMS cannot target subcortical areas and is a relatively invasive method which imposes other drawbacks on such a control group.

Given this limitation of the current control group, one could argue that for instance providing yoked feedback to the control group would be more suitable. This is unlikely to be the case as patients may realise that the feedback is not contingent on their mental strategies, especially if one particular strategy results in contradictory thermometer feedback at different moments in time. As the frustration that may be experienced as a result of this is likely to have a negative effect on depression severity, this control group comes with weaknesses of its own. In addition, it is unlikely that patients would be able to exercise physiological self-regulation over emotion areas when provided with yoked feedback as previous studies have shown the importance of valid feedback to master this task (see for instance DeCharms et al., 2005; Hamilton et al., 2011; Young et al., 2014).

Given the emotion regulation problems that depressed patients experience, it is noteworthy that patients in the EMO group managed to learn the self-regulation of their target area. Nevertheless, it did seem that continuous practise was required to maintain this ability. The inclusion of booster sessions might ensure getting the most out of neurofeedback as an add-on treatment for depression.

In terms of the overarching clinical trial, it is hypothesised that both groups will show an improvement in depression severity because both groups acquired up-regulation abilities. (The mediating role of perceived self-efficacy is examined in Chapter 7.) It is expected that the EMO group will show a larger improvement than the PPA group as the former group also targets abnormal brain activation levels associated with depression. Such an outcome would suggest that merely exposing patients to an MRI environment, providing rewarding feedback and expectancies generated by clinical trial participation do not induce improvements in depression. Because the dataset employed in the current chapter forms part of a currently ongoing clinical trial, the accuracy of these speculations will have to be awaited.

Chapter 6 - Neural networks mediating self-regulation via neurofeedback training in depression

6.1 Abstract

The current chapter investigated which areas mediated the neurofeedback task executed by depressed patients described in Chapter 5 and found involvement of for instance the dorsolateral prefrontal cortex (DLPFC), potentially involved in attentional processes, and areas involved in memory recollection such as the parahippocampal formation. Given the extensive interconnectivity in the brain, it is likely that neurofeedback training based on a single brain region indirectly affects a variety of other brain areas. Therefore it was also investigated how areas other than the target area, which was either an emotion processing area in the EMO group or the parahippocampal place area (PPA) in the PPA group, were affected by a course of five neurofeedback sessions. A two-way ANOVA with the factors *Group* and *Session* showed a main effect of group in the amygdala suggesting that the patients receiving feedback from emotion areas, but not the patients receiving feedback from the PPA, influenced a wider emotion regulation network. Many of the emotion processing areas that showed a significant *Group* x *Session* interaction showed deactivation during the first two sessions compared to the last two in the EMO group, potentially reflecting the initial difficulties experienced with generating positive emotions. Although this activation pattern could be expected in several of these areas that had often been selected as a target, a cluster in the bilateral thalamus showed a similar pattern. This may suggest that neurofeedback can target the limbic-thalamo-cortical circuit that has been implicated with depression.

6.2 Introduction

A plethora of brain areas involved in attention, memory, instrumental learning and imagery is expected to be activated during the up-regulation condition of

the neurofeedback task described in section 5.3.3. This chapter examines the neural networks mediating self-regulation via neurofeedback training. In addition, it investigates whether neurofeedback from positive emotion processing areas can target not only the individually selected target areas as described in Chapter 5, but also the neurobiological substrate of depression beyond these areas.

Dorsal anterior cingulate cortex (ACC) activation can be expected in relation to attentional processes (Lane, Fink, Chau, & Dolan, 1997) and striatal activation with regard to the instrumental learning component of the task (O'Doherty et al., 2004). The recollection and imagery of autobiographical memories is likely to be mediated by the hippocampus, parahippocampal formation, cuneus and precuneus (Cabeza & St Jacques, 2007). In addition to the target area, classical emotion processing areas are hypothesised to be activated in the EMO group (see section 5.3). Damasio et al. (2000) investigated which areas underlie recall and re-experience of intense positive autobiographical memories via positron emission tomography (PET). The successful induction of happiness was verified by a significantly different skin-conductance response, heart rate and intensity rating as compared to when recalling a neutral memory. A network of areas that keeps track of our internal state comprising the insula, secondary somatosensory cortex, cingulate cortex and hypothalamus was found to be activated during positive states. In addition, significant increases were found in the orbitofrontal cortex (OFC), striatum, hippocampus and parahippocampal region. The activation of the former two areas suggests that the recall of positive imagery was experienced as rewarding. It is likely that these areas will also be involved in the neurofeedback task due to its instrumental learning aspect. The latter two areas are also likely to play a role in the memory component of the neurofeedback task. As Damasio et al. (2000) compared positive with neutral autobiographical memory recollection no activation in areas associated with mental imagery, such as the cuneus, precuneus, visual cortex, fusiform gyrus and lingual gyrus, were reported. Johnston et al. (2011) and Linden et al. (2012) did find activation in the cuneus of healthy and depressed patients during a neurofeedback task involving positive emotion imagery, along with deactivation in the temporo-parietal junction (TPJ).

In correspondence with the process model of emotion regulation (see section 3.2) it is expected that after a patient in the EMO group selects a situation during the up-regulation condition, a comparable yet somewhat different combination of areas is involved. For instance, self-referential processing is likely to play a more important role in rumination compared to situation selection, hence the posterior cingulate is likely to take up a more prominent role (Brewer, Garrison, & Whitfield-Gabrieli, 2013). The attention aspect of rumination is likely to be mediated by the dorsolateral prefrontal cortex (DLPFC), ACC, precuneus and inferior parietal lobule (IPL). Rumination processes in healthy and depressed individuals do seem to differ, as rumination seems to require more effort in depressed patients (Cooney, Joormann, Eugène, Dennis, & Gotlib, 2010). At the neural level, rumination in depressed patients has been associated with a more pronounced involvement of the limbic system, as well as the medial and dorsal prefrontal cortex (Cooney et al., 2010). Increased and sustained activity in the amygdala has been consistently reported in rumination (Nolen-Hoeksema et al., 2008; Ray et al., 2005; Siegle, Ingram, et al., 2002), a finding which has been replicated in depressed patients (Siegle, Steinhauer, Thase, Stenger, & Carter, 2002). It must be noted that these findings investigated rumination in the classical sense, i.e. involving negative emotional material, while the emotional neurofeedback task in the current study has more resemblance with ruminating on positive emotions, a concept termed savoring (Bryant & Veroff, 2006; see section 3.3). Since for example the involvement of the amygdala has mainly been associated with tasks requiring to focus on negative affect (Cunningham, Raye, & Johnson, 2004, 2005), it is less likely to be involved during savoring. Nevertheless, both types contain similar elements with a potentially comparably similar neural substrate. Comparable to the situation selection aspect of the task, the posterior cingulate cortex, ventromedial prefrontal cortex (VMPFC), hippocampus and parahippocampus are expected to be involved for the retrieval of autobiographical memories (Maguire, 2001; Summerfield, Hassabis, & Maguire, 2009; Svoboda, McKinnon, & Levine, 2006). The rostral ACC, which seems to be involved when attending to subjective state (Lane et al., 1997), might also be involved. However, Kumari et al. (2003) found a decreased response in the rostral ACC

on a task involving the cognitive, yet externally mediated, generation of positive effect in depressed compared to healthy individuals. It is thus important to bear in mind that the assumptions about the brain areas likely to be involved in the neurofeedback task is mainly based on literature on healthy participants; activation patterns may deviate from these assumptions in patients with depression along the lines of the abnormal activation levels as described in section 1.2.2.

6.3 Methods

6.3.1 Participants

The date utilised in the current chapter originates from the same group of patients as described in section 5.3.1.

6.3.2 Data analysis

In order to investigate the network mediating self-regulation, a whole brain analysis of the self-regulation runs was conducted in BrainVoyager QX 2.3 (Brain Innovation, Maastricht, The Netherlands). The same pre-processing steps were taken as described in section 5.3.4 and included motion correction, temporal high pass filtering, spatial smoothing and temporal smoothing. All runs were aligned to the first volume of the localiser run and transformed into Talairach space (Talairach & Tournoux, 1988). The physiological measures, heart and respiratory rate, and motion confounds were included as covariates in the random-effects general linear model (GLM). No whole brain analysis of the localiser runs was conducted as the current thesis focuses on the pathways via which neurofeedback training could potentially alleviate depression.

6.4 Results

A whole brain analysis was conducted collapsed across groups to uncover the network mediating the self-regulation (Table 6.1). The activation map was thresholded at $p < .001$ and cluster threshold corrected. Clusters of significant activation were present in for instance the dorsomedial prefrontal cortex (DMPFC), posterior cingulate (Figure 6.1A), ventrolateral prefrontal cortex (VLPFC) and parahippocampal gyrus (Figure 6.1B). No clusters showing significant deactivation were present.

Self-regulation mediating network (p = .001, cluster threshold corrected)		
Nr of Voxels	***TAL coordinates***	***Area***
1546	-7,4,66	L DMPFC
500	-40,-2,57	L DLPFC
1714	-31,25,6	L VLPFC bordering ant insula
2495	-34,-38,-9	L Hippocampal formation
416	20,-32,-15	R Hippocampal formation
341	14,-41,9	R Posterior cingulate
2366	-7,-53,6	L Posterior cingulate
1634	-16,64,27	L Ant medial prefrontal gyrus
478	-28,22,58	L SFS

Table 6.1. Overview of areas significantly more activated during the up-regulation condition compared to the count condition. TAL = Talairach, R = right, L = left, ant = anterior, DLPFC = dorsolateral prefrontal cortex, VLPFC = ventrolateral prefrontal cortex, SFS = superior frontal sulcus.

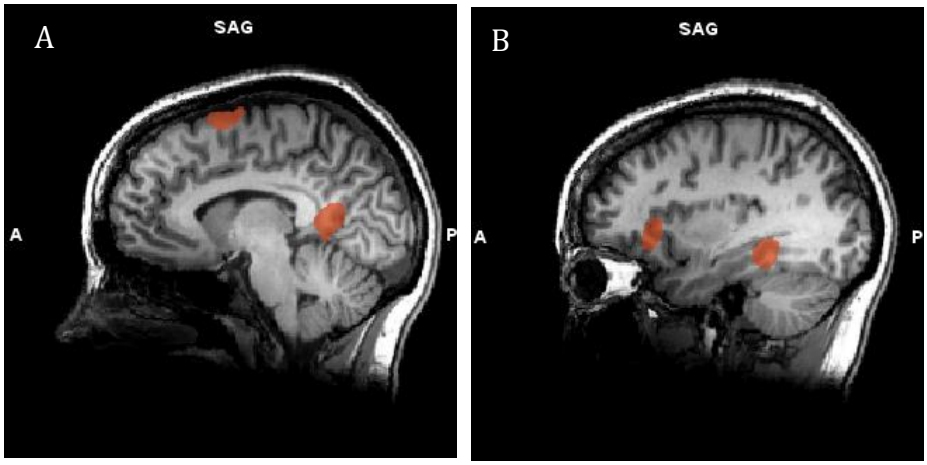

Figure 6.1. A) Clusters in the left DMPFC and posterior cingulate were activated during the up-regulation condition. B) The same holds for clusters in the left VLPFC and parahippocampal gyrus.

A two-way ANOVA with the factors *Group* (EMO/PPA) and *Session* (Early/Late) was computed at the whole brain level. The data making up early sessions were composed of session one and two, the late session dataset comprised session four and five. Activation maps were thresholded at $p < .05$ and cluster threshold corrected. Areas showing a main effect of *Group* are listed in Table 6.2, areas showing a main effect of *Session* in Table 6.3 and the areas showing an interaction between *Group* and *Session* in Table 6.4. The PPA did not show a main effect of group as this area was also activated during the late sessions in the EMO group. The activation in the areas showing a main effect of *Session* was higher during late compared to early sessions, with the exception of a cluster in the anterior medial prefrontal gyrus that was more activated during early sessions.

Clusters showing a significant main effect of Group (p = .05, cluster threshold corrected)			
Nr of Voxels	***TAL coordinates***	***Area***	***Higher activation in***
8902	32, 7, 51	R DLPFC	PPA group
1836	11, 64, 12	R Ant medial frontal gyrus	PPA group
1673	48, -65, 27	R STG	PPA group
939	-7, -2, 57	L DMPFC	EMO group
1072	-19, 7, -21	L Amygdala	EMO group
1350	-31, -44, 15	L Heschl's gyrus	EMO group
2093	2, -92, -9	R Occipital cortex	EMO group

Table 6.2. Overview of areas showing a main effect of Group. TAL = Talairach, R = right, L = left, ant = anterior, DLPFC = dorsolateral prefrontal cortex, STG = superior temporal gyrus, DMPFC = dorsomedial prefrontal cortex.

Clusters showing a significant main effect of Session (p = .05, cluster threshold corrected)			
Nr of Voxels	***TAL coordinates***	***Area***	***Higher activation during***
1499	36, 1, 54	R DLPFC	Late sessions
7196	50, 26, 27	R VLPFC	Late sessions
1976	32, -53, -6	R Parahippocampal gyrus	Late sessions
10442	-37, -41, -6	L Parahippocampal gyrus	Late sessions
1601	-13, 61, 21	L Ant medial frontal gyrus	Early sessions
6651	17, -5, 15	R Dorsal striatum	Late sessions
4217	-64, -26, 21	L TPJ	Late sessions
1203	-49, 4, -6	L STG	Late sessions
1918	-25, -32, 63	L Post-central gyrus	Late sessions
3917	-37, -65, 36	L Precuneus	Late sessions
14563	-22, -2, 15	L Paracentral lobule	Late sessions

Table 6.3. Overview of areas showing a main effect of Session. TAL = Talairach, R = right, L = left, ant = anterior, DLPFC = dorsolateral prefrontal cortex, VLPFC = ventrolateral prefrontal cortex, TPJ = temporoparietal junction, STG = superior temporal gyrus.

A significant interaction between *Group* and *Session* was observed in many areas involved in emotion processing, such as the ventro- and dorsolateral PFC and striatum (Figure 6.2). The activation pattern in all clusters in the VLPFC and DLPFC was roughly similar. While these areas were deactivated during early sessions in the EMO group, they were activated in the PPA group. During later sessions, the opposite pattern was measured with activation occurring in the EMO group and deactivation in the PPA group. The activity in the insula on the other hand increased somewhat in the PPA group over time, but increased more in the EMO group. Although the activity in the cluster encompassing the thalamus and right dorsal striatum decreased slightly over time in the PPA group, the activation levels remained positive during late sessions. In the EMO group a similar pattern as observed in prefrontal clusters was measured, with deactivation during early session and activation during late sessions. A large cluster that encompassed the posterior cingulate, TPJ and parahippocampal gyrus was actually activated during early sessions in the EMO group but was activated more during late sessions. In the PPA group the activation levels decreased but remained positive over time. The activation in the DMPFC followed the exact same pattern as in this large cluster.

Clusters showing a significant Group x Session interaction (p = .05, cluster threshold corrected)		
Nr of Voxels	***TAL coordinates***	***Area***
9120	38, 10, 24	R VLPFC/DLPFC
5476	-49, 16, 33	L VLPFC/DLPFC
7346	51, 25, 3	R VLPFC
3458	-55, 31, 12	L VLPFC
18764	-4, 10, 63	L DMPFC
2448	35, 1, 0	R Insula
6769	17, -11, 15	R Dorsal striatum / Bil Thalamus
50360	20, -68, -3	Bil Posterior cingulate, L TPJ, R Parahippocampal gyrus
5079	8, -35, 57	R Paracentral lobule
6403	-34, -23, 42	L Post-central gyrus
1463	44, -38, -6	R MTG
1799	-67, -35, 0	L MTG

Table 6.4. Overview of areas showing an interaction between Group and Session. TAL = Talairach, R = right, L = left, bil = bilateral, ant = anterior, VLPFC = ventrolateral prefrontal cortex, DLPFC = dorsolateral prefrontal cortex, DMPFC = dorsomedial prefrontal cortex, TPJ = temporoparietal junction, MTG = middle temporal gyrus.

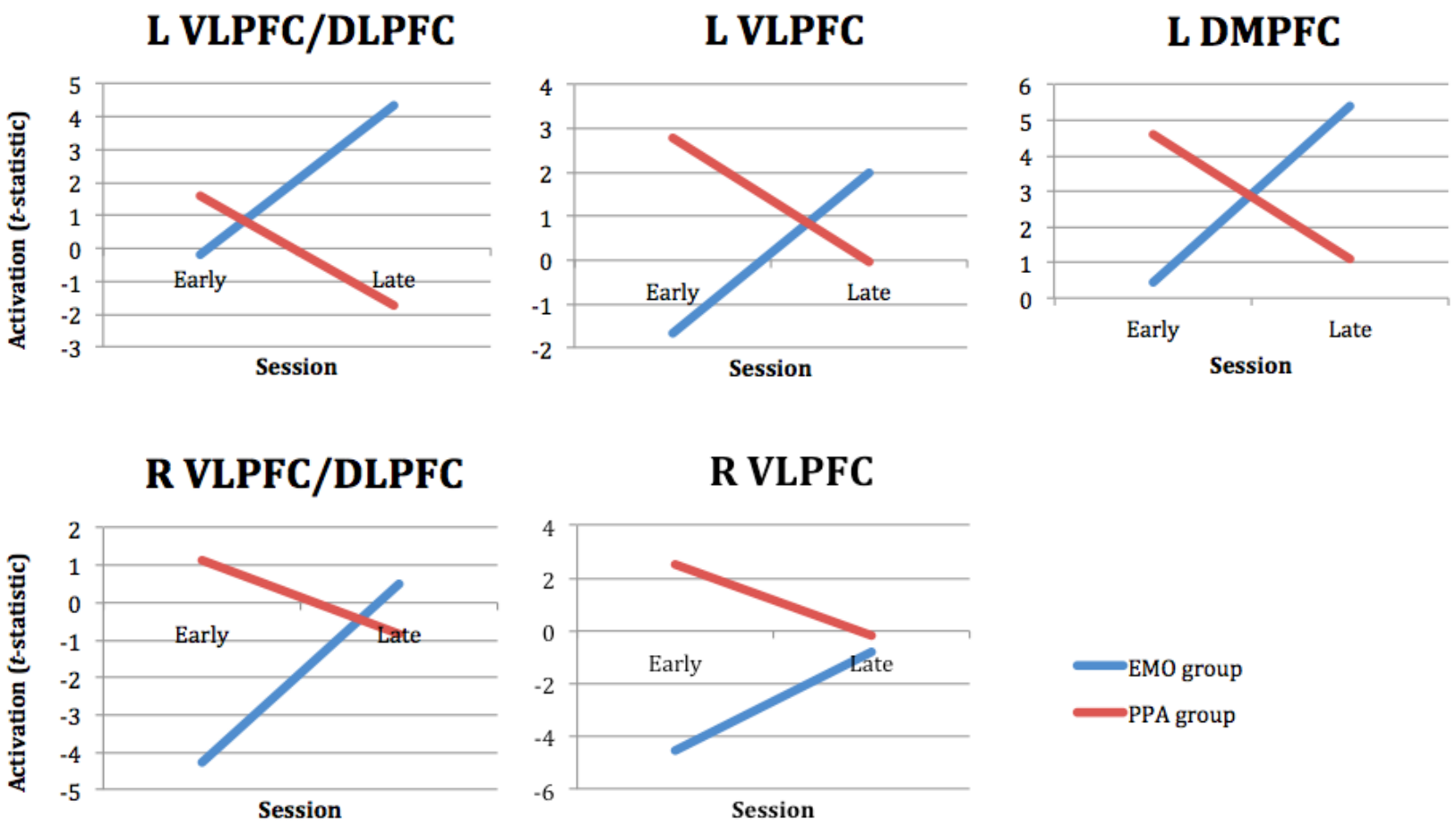

Figure 6.2. Activation patterns in the areas showing a significant interaction between Group and Session. Early sessions comprised session one and two, late sessions comprised session four and five. R = right, L = left, bil = bilateral, VLPFC = ventrolateral prefrontal cortex, DLPFC = dorsolateral prefrontal cortex, DMPFC = dorsomedial prefrontal cortex, TPJ = temporoparietal junction.

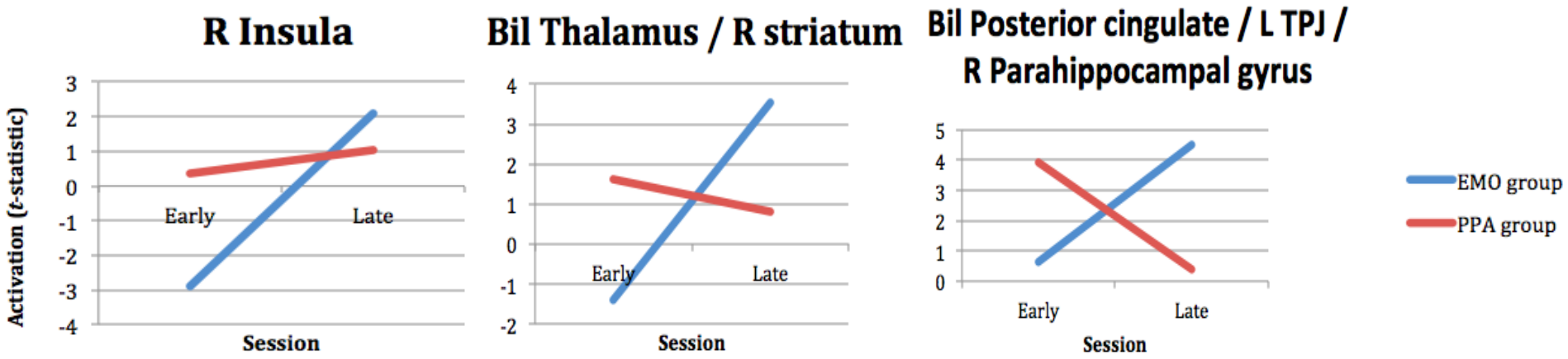

Figure 6.2 Continued.

6.5 Discussion

The current chapter investigated brain activation associated with neurofeedback training at the whole brain level. As expected increments in brain activation were not confined to the selected target areas and areas putatively involved in the situation selection and savouring aspect of the task were activated as well (see section 3.2 for a background on postulated task components based on the process model of emotion regulation). Attentional processes may have driven the activity in the DLPFC in both groups and memory recollection the activation of the parahippocampal formation and DMPFC (Summerfield et al., 2009; Svoboda et al., 2006). The posterior cingulate was active in both groups, suggesting that not just patients in the EMO group engaged in the recollection of autobiographical memories and self-referential processing (Brewer et al., 2013). While the PPA is responsive to both new and familiar environments, it is more likely that patients in the PPA group selected scenes that carried a personal value to them as their task was to imagine relaxing places. The higher cognitive functions that the neurofeedback task required may have resulted in the involvement of the anterior medial PFC. This area has also been implicated in self-referential processing and attention (Zysset, Huber, Samson, Ferstl, & von Cramon, 2003). The active clusters in the VLPFC, DLPFC and insula were not driven by the EMO group as no main effect of *Group* was found for these clusters. Instead, the anterior insula may have been involved with internal state monitoring and the VLPFC with the production of a positive or relaxed state in the EMO and PPA group respectively. In turn, the DLPFC may have played a role in monitoring this self-regulation process. Alternatively, the DLPFC may have mediated the inward-directed attentional component of savoring that was potentially required to sustain a certain strategy over the 20 s of each up-regulation condition (see section 3.3).

The activation of the PPA in the EMO group during the last sessions might be related to patients recalling autobiographical memories with a strong scenic component. This raises the question why patients adopted this strategy only during late, but not during early, sessions. One possibility is that patients

realised via the feedback that merely thinking about a certain person or event did not result in the greatest increase in target area activation. Instead, patients may have found out that if they attempted to envisage a certain person or relive a certain event including all the surroundings, this was more powerful to drive the activation in the target area upwards.

Although the main effect of *Session* in a cluster in the dorsal striatum suggested that the last two sessions were experienced as more rewarding than the first two, this is unlikely to be mediating the activation pattern in this particular cluster. Although the up-regulation ability of both groups combined was higher during the last two sessions, the up-regulation performance in the PPA group was actually lower during late compared to early sessions (see section 5.4). An interaction effect would thus have been expected instead. This was indeed found in another cluster in the striatum, which extended into the thalamus (Figure 6.3). The pattern in this cluster corresponds to the assumption that when patients were presented with a larger amount of positive feedback this was experienced as more rewarding, along with a higher sense of achievement.

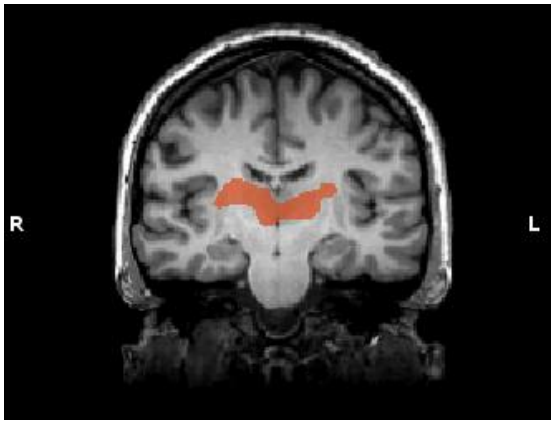

Figure 6.3. A significant interaction between the factors *Group* and *Time* was found in this cluster in the striatum, with activation extending into the thalamus. This activation pattern may reflect that positive feedback was experienced as rewarding.

The deactivation observed in many emotion processing areas during early sessions in the EMO group may reflect the difficulty that patients initially experienced with generating positive emotions. An improvement in this ability was in turn associated with activation in these areas during late sessions. With respect to these late sessions, these emotion processing areas were more

activated in the EMO than PPA group. While the VLPFC, DLPFC and insula were commonly chosen target areas (see section 5.4) and this activation pattern could thus be expected, the bilateral thalamus was not selected as a target area in any of the patients. This suggests that neurofeedback training has the ability to target the limbic-thalamo-cortical circuit that has been implicated with depression (Drevets, 2001; Rigucci, Serafini, Pompili, Kotzalidis, & Tatarelli, 2010) both directly and indirectly. The finding that the amygdala was only activated in the EMO group also supports this speculation.

Although the ACC, and in particular the subgenual ACC, has been postulated to play a vital role in depression, the neurofeedback training did not seem to have involved this area. This parallels findings of Kumari et al. (2003) who found that unlike healthy individuals, depressed patients showed a deactivation of the rostral ACC during positive emotion induction via picture-caption pairs. This may extend to internally generated positive emotions. Moreover, in depression a reduced connectivity has been found between the ACC on the one hand and the thalamus, striatum and amygdala on the other (Anand et al., 2005; Caspi et al., 2003). This may explain why neurofeedback training was unable to affect this area.

Compared to Linden et al. (2012) a similar network of areas was activated during the neurofeedback task, although no areas were found to be deactivated in the current study. This does match the finding of Sheline et al. (2009) and Grimm, Boesiger, et al. (2008) who did not find the expected decrease in activation in the default-mode network (DMN) during affective tasks in depressed patients. Another difference with the pilot study was that more areas were found to be activated during late than early sessions. It must be noted that some important differences exist between both studies, such as the time span of the study and the inclusion of a scanned control group, which may be reflected in imaging data differences. Nevertheless the current data also seem to suggest that the neurofeedback task was experienced as more rewarding when up-regulation performance was higher.

The findings presented in this chapter suggest that neurofeedback has the capability to target a wider emotion processing network than merely the individually selected target areas. As this network includes brain areas forming part of the limbic-thalamo-cortical circuit for instance, it is likely that neurofeedback targets areas playing a crucial role in the initiation and continuation of depression.

Chapter 7 – The effect of neurofeedback training on self-efficacy in depression

7.1 Abstract

Albert Bandura's self-efficacy theory postulates that the motivation to engage in certain behaviours depends on the expectations of the individual regarding the likelihood that the desired outcome will be achieved. According to this theory, depression is mediated in part by perceived inefficacy regarding thought control. An enhanced sense of thought control efficacy could reduce the intrusiveness of negative thoughts experienced, thereby improving depression. Real-time functional magnetic resonance imaging (fMRI) neurofeedback has the potential to instil heightened perceived thought control self-efficacy by providing objective insight into the effect of thought processes on brain activation. The current study investigated whether a course of five fMRI neurofeedback sessions improved self-efficacy in a sample of sixteen moderately to severely depressed patients. The improvements on a thought control questionnaire and a thought control ability questionnaire only just failed to reach significance. The improvement on a self-efficacy scale which measured behavioural changes resulting from changes in thought control was highly significant. Interestingly, patients with a relatively high depression score combined with a relatively low perceived thought control ability score at baseline seemed to benefit the least, which stresses the importance of early diagnosis and treatment of depression. The current study did not investigate whether the neurofeedback training resulted in improvements in depression as the current dataset is an excerpt of a larger dataset of a currently still running clinical trial.

7.2 Introduction

The main aim of the clinical trial of which the current thesis lends a partial dataset, is to investigate whether neurofeedback training results in a clinical improvement of depression. Chapter 5 investigated whether neurofeedback could accomplish this via targeting a brain area involved in the processing of positive emotions. Chapter 6 also investigated whether neurofeedback can target the abnormal neurobiology associated with depression by examining any concomitant whole brain activation changes. The current chapter assesses whether neurofeedback can influence the maladaptive cognitive processes linked to depression, with a focus on self-efficacy (see section 1.2.1). Several studies have demonstrated a relationship between self-efficacy and depression. Kavanagh & Wilson (1989) for instance found that in healthy participants lower scores on various measures of self-efficacy were correlated with higher scores on Beck's Depression Inventory (BDI; Beck, Rush, Shaw, & Emery, 1987). In the same study, the authors administered cognitive therapy to depressed patients and found that enlarged perceived self-efficacy predicted clinical improvement. Moreover, self-efficacy scores at 12-month follow-up predicted symptom remission. Because the current clinical trial is presently still ongoing, this chapter does not examine any changes in depression severity following neurofeedback training. Instead, this chapter investigates the effect of neurofeedback training on self-efficacy (see Chapter 1 for background information on self-efficacy and depression). It also investigates whether there is any relation between up-regulation ability (see Chapter 5) and self-efficacy. It was expected that both groups would develop a heightened sense of self-efficacy as patients in both groups experienced gaining control over their target area (see section 5.4). It was also expected that the better someone performed during the neurofeedback training, the larger the increase in self-efficacy score would be.

7.3 Methods

7.3.1 Participants

Data from the same group of patients as described in section 5.3.1 was used.

7.3.2 Materials

The MINI (Sheehan et al., 1998) was administered at the start of the trial to confirm the diagnosis of current depression and to assess comorbidity. The Hamilton Depression Rating Scale (HDRS; Hamilton, 1960) was administered by a psychologist or psychiatrist blind to group assignment. Only patients with a HDRS score of 14 or higher were included in the study. One exception was made for the first patient in the PPA group who had a HDRS score of 12 but had a score of 26 on the BDI, suggesting that it was appropriate to include this patient. As the HDRS is the main dependent measure of the ongoing clinical trial, HDRS scores were not included in the following analysis. The BDI was included as an additional measure of depression severity and was, for similar reasons, only analysed collapsed across both groups. The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) was included to obtain a measure of both depression and anxiety.

Three measures of self-efficacy were administered. The Thought Control Questionnaire (TCQ; Wells & Davies, 1994) was included to provide insight into commonly used strategies to control unwanted thoughts. While the TCQ measures the extent to which advantageous thought control strategies are used, the Thought Control Ability Questionnaire (TCAQ; Luciano, Algarabel, Tomás, & Martínez, 2005) measures the extent to which participants feel they are in control over their own (intrusive) thoughts. To investigate whether any changes in cognitive control would translate into behavioural changes, the Self-Efficacy Scale (SES; Sherer et al., 1982) was included too and measured general and social self-efficacy.

The Profile of Mood State (POMS; McNair, Lorr, & Droppleman, 1992), a 65-item questionnaire requiring the rating of mood-related keywords, was administered immediately before and after each neurofeedback scan to capture any immediate changes in mood state.

7.3.3 Procedure

Apart from the MINI and POMS, all measures were obtained at start (baseline assessment), after five neurofeedback sessions (post assessment) and at follow-up, which took place one month after the final neurofeedback scan. The MINI was only conducted at baseline (to confirm diagnosis) and the POMS was conducted before and after each imaging session.

7.3.4 Data analysis

The data analysis was conducted in accordance with a pre-planned analysis protocol approved by the South East Wales Trials Unit (SEWTU) and was performed in SPSS 20 (SPSS Inc., Chicago, IL, USA). All the variables were normally distributed (Kolmogorov-Smirnov test, all *p*s > .1) Data reduction was performed on the constructs depression and self-efficacy. Whenever a questionnaire was made up of several subscales, the scores of these were added up to produce an overall score.

7.4 Results

7.4.1 Preparatory data analysis

It was expected that both the EMO and PPA group would show an increase in self-efficacy as both groups attained comparable up-regulation skills (see section 5.4). Therefore the scores on the BDI, HADS, SES, TCQ and TCAQ were collapsed across group to increase power. This approach was justified by the absence of baseline differences between both groups (all *p*s > .3).

Data reduction steps were taken to minimise issues related to multiple testing. The reliability of all scales was determined by calculating Cronbach's alpha via

the baseline scores of both groups combined. All scales scored a reliability of .7 or higher (Table 7.1). After the reliability of the BDI and HADS were confirmed, spearman's correlation coefficient was calculated (*rho* = .810, $p < .001$). Given the high correlation between both measures an aggregate score for depression was computed. For this purpose both scores were *z*-transformed and summed to produce the variable 'DepressionTotal'. The correlations between the meta-cognitive measures SES, TCAQ and TCQ were all weak and non-significant (all *p*s > .2). Therefore, no composite score was generated for self-efficacy. Instead, the scores on each individual scale were used in the analysis.

Scale	Cronbach's alpha
BDI	.862
HADS (subscales combined)	.883
TCQ (subscales combined)	.746
TCAQ	.905
SES (subscales combined)	.759

Table 7.1. Reliability of the different questionnaires assessed with Cronbach's alpha.

7.4.2 Exploratory data analysis

First, some exploratory statistical tests were run to confirm the validity of Bandura's self-efficacy theory. If its assumptions are correct, a significant difference would be expected between the self-efficacy scores of depressed patients and healthy volunteers. The baseline TCQ and TCAQ scores of all patients in the current depression study were therefore compared with the scores of the volunteers participating in the perception study described in Chapter 4. An independent samples *t*-test confirmed that the TCAQ scores in that sample ($M = 85.65$, $SE = 3.088$) were significantly higher than in the sample of depressed patients ($M = 57.75$, $SE = 3.646$; $t(31) = 5.863$, $p < .001$). The same applied to the TCQ scores in that sample ($M = 63.76$, $SE = 1.363$) compared to the depressed sample ($M = 58$, $SE = 3.646$; $t(31) = 2.315$, $p = .027$). However, it must be noted that the volunteers in the depression study were significantly older ($t(31) = 9.985$, $p < .001$) and that no mental health questionnaire was administered in the perception study to rule out mental health disorders.

7.4.3 The relation between self-efficacy and cognitive/physiological self-regulation

In order to investigate whether neurofeedback training indeed increased self-efficacy, paired *t*-tests were computed to compare the scores at baseline and post assessment. The increase in TCQ ($t(15) = -1.851$, $p = .084$; Figure 7.1A) and TCAQ score ($t(15) = -1.867$, $p = .082$; Figure 7.1B) only just failed to reach significance. The increase in SES was highly significant ($t(15) = -4.374$, $p = .001$; Figure 7.1C).

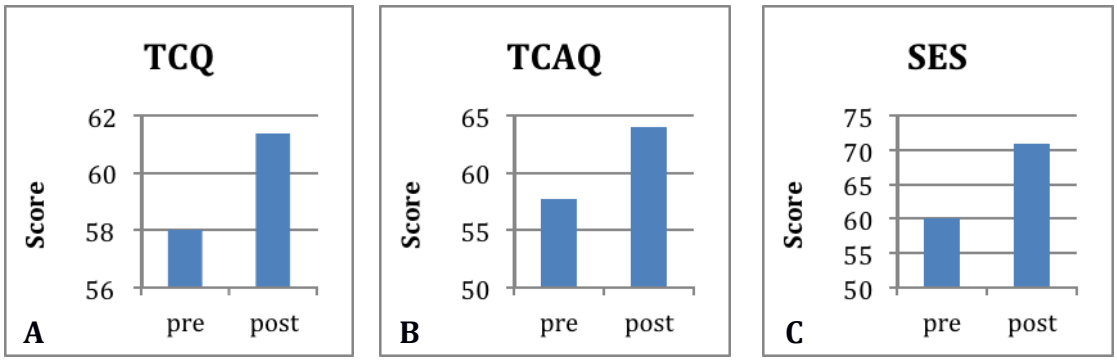

Figure 7.1. A-B) Improvements in TCQ and TCAQ scores after a course of five neurofeedback sessions only just failed to reach significance, C) while the improvement on the SES was highly significant.

If a higher up-regulation ability is related to a higher sense of self-efficacy, then Bandura's self-efficacy theory would predict that patients who perform well on the neurofeedback task will have lower depression severity scores. In accordance, a significant negative correlation was found between neurofeedback ability and 'DepressionTotal' at post assessment ($r = -.508$, $p = .045$; Figure 7.2). Conversely, no significant correlation was found between up-regulation performance on the one hand and TCQ ($p = .74$), TCAQ ($p = .688$), and SES ($p = .875$) score at post assessment on the other. This finding does not necessarily go against the predictions made by self-efficacy theory, as the theory stresses the importance of *perceived* self-efficacy (opposed to actual self-regulation skills). Therefore, the potential relation between depression severity and the self-efficacy measures was investigated next.

At baseline, no correlations were found between 'DepressionTotal' on the one hand and TCQ and SES on the other (both *p*s > .5). However, a significant negative correlation was found between 'DepressionTotal' and TCAQ at baseline (r = -.542, p = .03; Figure 7.3) and after five neurofeedback sessions (r = -.665, p = .005; Figure 7.4). It must be taken into account that these significant findings might not reflect a true correlation between 'DepressionTotal' and TCAQ and instead may be a consequence of the multiple comparisons conducted, which inflate type I errors. The data points below the dashed line in Figure 7.3 and 7.4 represent the same four patients on both graphs. This might suggest that neurofeedback training induces little change if patients have a relatively high initial depression score combined with a relatively low initial TCAQ score.

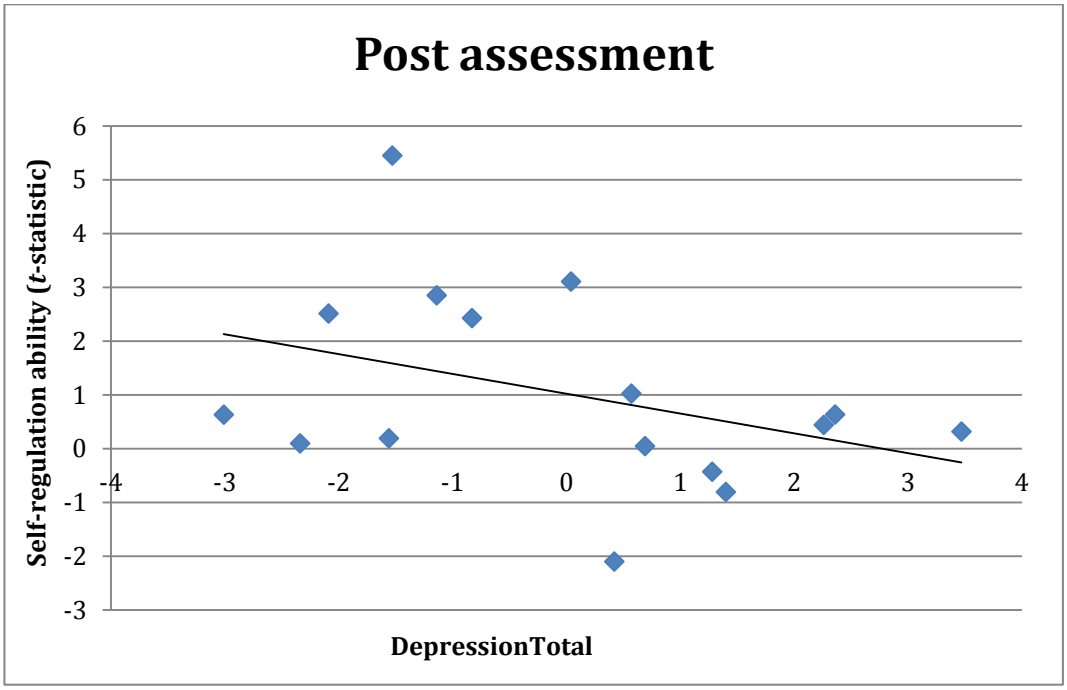

Figure 7.2. Relation between depression severity and up-regulation performance at post assessment. Each data point represents a patient. DepressionTotal represents the aggregate score computed from the BDI and HADS questionnaire.

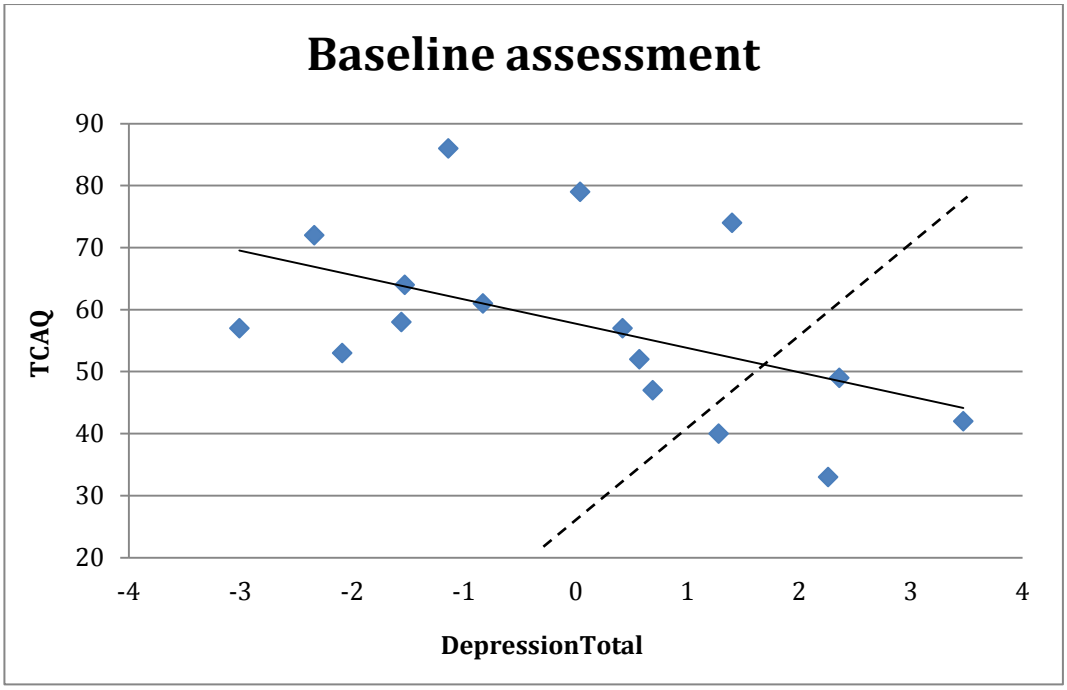

Figure 7.3. Relation between depression severity and perceived self-efficacy of thought control at baseline. Each data point represents a patient. DepressionTotal represents the aggregate score computed from the BDI and HADS questionnaire.

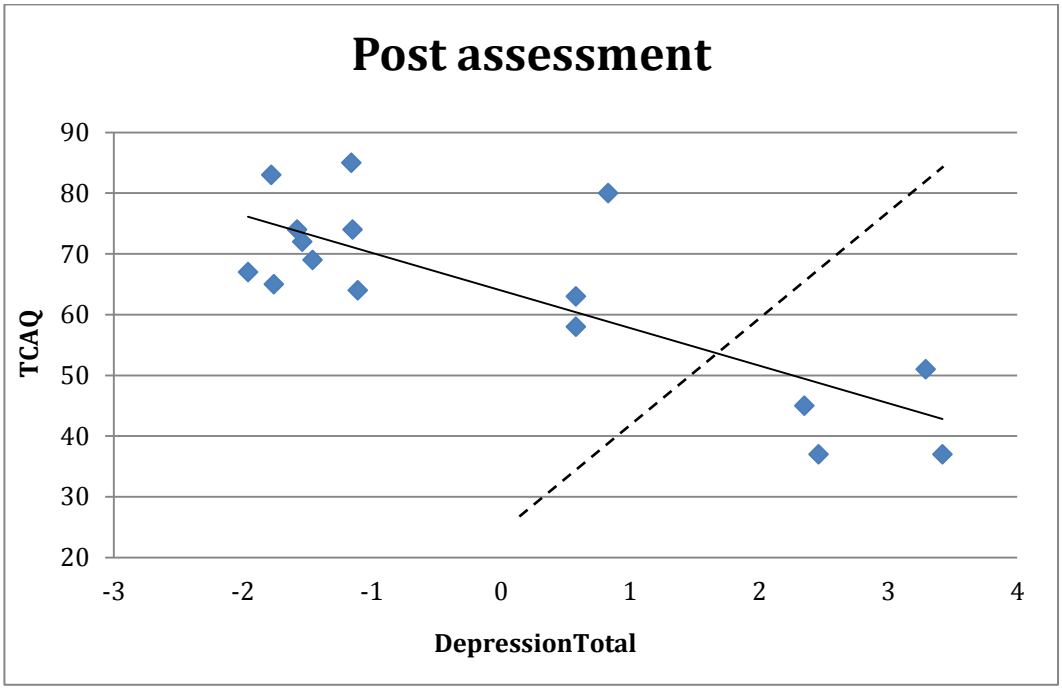

Figure 7.4. Relation between depression severity and perceived self-efficacy of thought control at post assessment. Each data point represents a patient. DepressionTotal represents the aggregate score computed from the BDI and HADS questionnaire.

A one-sample *t*-test showed that there was a significant decrease in the Total Mood Disturbance (TMD) scores, derived from the POMS, after each neurofeedback session ($t(63) = -4.731$, $p < .001$). For none of the four neurofeedback sessions a correlation between change on the POMS and the presented reward rate was found (all ps > .7). A significant drop in TMD scores was also found during the transfer session ($t(15) = -3.993$, $p = .001$). These two findings suggest that the presentation of positive feedback on its own does not induce mood improvements and is unlikely to result in specific improvements in depression.

7.5 Discussion

Our data suggest that neurofeedback training induces a higher sense of self-efficacy. Self-efficacy theory predicts that as a consequence patients may expect to be more successful in controlling their thoughts and are therefore more likely to attempt to do so. It must be noted that patients who had a relatively high depression score in combination with a relatively low perceived thought control ability score at baseline seemed to benefit little from the neurofeedback procedure. This suggests that an initial amount of perceived self-efficacy of thought control might be required to generate more self-efficacy confidence in the long term and to improve depression. Therefore, it might be of interest to investigate whether neurofeedback can play a preventative role in the development of depression. It should be noted that the current study does not allow making any inferences of causality as it could be that improvements in mood, as indicated by the POMS, resulted in patients feeling more adequate in controlling their cognitions.

No significant correlation was found between any of the self-efficacy measures and up-regulation performance at post assessment. As self-efficacy theory predicts, this suggests that there is an important distinction between *perceived* self-efficacy, as measured by for instance the TCAQ, and actual self-regulation skills as measured by up-regulation ability. However, patients who performed

better on the neurofeedback task did tend to have lower depression scores at post assessment. It is not clear what mediates this relation. The role of the specific neurobiological component targeted by neurofeedback is still unclear as this analysis had to be collapsed across group.

The neurofeedback training seemed to induce relatively direct improvements in mood, as significantly lower TMD scores were obtained after each neurofeedback run. It is unlikely that the presented feedback induced these mood changes by being experienced as rewarding, as no correlation between reward rate and TMD score was found. The reason why patients experienced a positive improvement in mood during the transfer session remains elusive. Patients did not manage to up-regulate their target area during this session (see section 5.4) and were not presented with any feedback that could have installed a sense of self-regulation mastery. It is doubtful that patients experienced relief after leaving the relatively confined and noisy environment of the scanner as none of the patients, apart from one drop out, reported any discomfort. It could be possible that the mere completing of a session made patients feel better about themselves or that the imagery of either positive emotions or relaxing environments left patients feeling less disturbed.

Although issues surrounding multiple testing were prevented as much as possible by executing data reduction steps wherever appropriate, the current analysis may still suffer from inflated type I errors. As a consequence the results should be interpreted with caution but are nevertheless of interest in this exploratory analysis.

Chapter 8 - Pattern classification of valence in depression

This chapter has been accepted for publication in NeuroImage: Clinical and the co-authors of the paper are Sarah Krall (joint first author), Dr Stephen Johnston, Dr Kenneth Yuen, Dr David Healy, Prof Rainer Goebel, Dr Bettina Sorger and Prof David Linden.

8.1 Abstract

Neuroimaging biomarkers of depression have potential to aid diagnosis, identify individuals at risk and predict treatment response or course of illness. Nevertheless none have been identified so far, potentially because no single brain parameter captures the complexity of the pathophysiology of depression. Multi-voxel pattern analysis (MVPA) may overcome this issue as it can identify patterns of voxels that are spatially distributed across the brain. Here we present the results of an MVPA to investigate the neuronal patterns underlying passive viewing of positive, negative and neutral pictures in depressed patients. A linear support vector machine (SVM) was trained to discriminate different valence conditions based on the functional magnetic resonance imaging (fMRI) data of nine unipolar depressed patients. A similar dataset obtained in nine healthy individuals was included to conduct a group classification analysis via linear discriminant analysis (LDA). Accuracy scores of 86% or higher were obtained for each valence contrast via patterns that included limbic areas such as the amygdala and frontal areas such as the ventrolateral prefrontal cortex. The LDA identified two areas (the dorsomedial prefrontal cortex and caudate nucleus) that allowed group classification with 72.2% accuracy. Our preliminary findings suggest that MVPA can identify stable valence patterns, with more sensitivity than univariate analysis, in depressed participants and that it may be possible to discriminate between healthy and depressed individuals based on differences in the brain's response to emotional cues.

8.2 Introduction

Brain imaging studies have traditionally relied on the analysis of the univariate responses of individual voxels in the brain to differing conditions. However, multivariate analyses that incorporate dependencies between multiple voxels (Norman, Polyn, Detre, & Haxby, 2006) may be more appropriate for the functional architecture of the human brain, which is characterised by distributed information processing (Haxby et al., 2001; Pinel, Piazza, Le Bihan, & Dehaene, 2004). Multi-voxel pattern analysis (MVPA) has the ability to detect patterns at a finer resolution, with weaker activations, where they are part of a collective representation of a certain task condition or mental state. Previous studies have applied MVPA for example to detect perceptual (e.g. Haxby et al., 2001; Mourão-Miranda et al., 2005) or cognitive states (e.g. Davatzikos et al., 2005; Haynes and Rees, 2005), predict disease (e.g. Craddock et al., 2009; Zhang et al., 2005; Zhu et al., 2005; Mourão-Miranda, Almeida, et al., 2012; Mourão-Miranda, Oliveira, et al., 2012) or affective states (Yuen et al., 2012), identify dysfunctional processes in clinical populations (e.g. Yoon et al., 2008) and for clinical response prediction (e.g. Costafreda et al., 2009).

8.2.1 Studying emotion processing with MVPA

It has been argued that MVPA has superior sensitivity for determining patterns of response compared to univariate methods (De Martino et al., 2008; Hanke et al., 2009; Norman et al., 2006; Yoon et al., 2008). This makes it particularly appealing for emotion research. Emotion processing is assumed to involve a widely distributed network of limbic and prefrontal areas (Damasio, 1998). Its brain correlates have been studied in humans using different models of affect which can be classified as categorical (e.g. Roseman et al., 1990; Ekman, 1992) or dimensional (e.g. Schachter and Singer, 1962). Neuroimaging studies (particularly in combination with MVPA) have the potential to resolve the ongoing debate between both classes of models. Categorical models regard emotions as discrete entities that can be expected to be mediated by distinct brain areas and revealed by univariate analysis. In contrast, dimensional models describe emotions via their placement on two or more dimensions. In terms of

brain activation, this would be reflected in changes in the balance of activation between different areas, which can only be picked up by multivariate analyses. In this paper we implemented one of the most influential dimensional models that is based on the emotion circumplex (Russell, 1980) and assumes that emotional states can be described via a combination of arousal (the extent of activation one experiences) and valence (the extent of pleasantness one experiences). In terms of brain imaging, this can be utilised to compute contrasts between different types of affective stimuli and neural correlates of emotions. Previous studies with univariate methodology have shown substantial overlap between the cortical regions that process positive, negative and neutral affect (Johnston, Boehm, Healy, Goebel, & Linden, 2010; Murphy, Nimmo-Smith, & Lawrence, 2003; Phan, Wager, Taylor, & Liberzon, 2002), suggesting that univariate/ categorical models may not fully capture the complexity of emotion processing in the human brain. Conversely, MVPA studies have suggested that multivariate analysis may be sensitive to differences in neuronal patterns underlying different levels of valence in healthy volunteers (Baucom, Wedell, Wang, Blitzer, & Shinkareva, 2012; Yuen et al., 2012). In the study by Baucom et al. (Baucom et al., 2012), one classifier predicted whether participants had viewed positive or negative pictures evoking high or low arousal and another discriminated between positive and negative valence. These classifiers reached a maximum within-participant accuracy of 77% and 92% respectively.

8.2.2 MVPA and pathological emotion processing in depression

Functional imaging has elucidated the brain networks associated with altered emotion processing in affective disorders (Phillips et al., 2003b) and has revealed changes in neural activation both in symptomatic and remitted states (Goldapple et al., 2004; Siegle, Steinhauer, et al., 2002). Neuroimaging biomarkers would be of interest to improve diagnosis, for example in the differentiation between unipolar and bipolar depression, or as trait markers of risk for mood disorder in vulnerable individuals (Linden, 2012), and MVPA may be particularly useful for this purpose (Mourão-Miranda, Oliveira, et al., 2012) because no single parameter of brain structure or activation can capture

the complexity of the pathophysiology of depression. Such biomarkers would also be potentially useful as predictors of treatment response, for treatment stratification or as surrogate markers in clinical trials (Keedwell & Linden, 2013). Several previous studies have applied MVPA in the context of depression (Fu et al., 2008; Hahn et al., 2011; Marquand, Mourão-Miranda, Brammer, Cleare, & Fu, 2008). In one study individuals were classified as healthy or depressed (with 86% accuracy) based on the pattern of cortical activity representing the implicit processing of sad facial expression (Fu et al., 2008). Another study applied pattern recognition to the functional magnetic resonance imaging (fMRI) data of healthy and depressed individuals who completed two versions of the monetary incentive delay task and passively viewed facial expression (Hahn et al., 2011). A combination of the conditions involving neutral faces, receiving large rewards and anticipating no loss resulted in the highest group classification accuracy.

8.2.3 Current study

To our knowledge no study has investigated whether it is possible to accurately identify specific valence conditions in response to International Affective Picture System (IAPS; Lang et al., 1997) pictures in brain activation data from depressed patients, which thus formed the main aim of the current study. While (Mourão-Miranda, Almeida, et al., 2012) investigated the discriminability of patterns that underlie viewing happy and neutral faces in unipolar and bipolar depressed patients, the current study focused on unipolar depression, was not confined to the processing of facial expressions and included negative valence cues as well. Patients suffering from depression were presented with an emotion localiser composed of positive, negative and neutral images. A support vector machine (SVM) was trained to classify the data as belonging to one of the three picture valence categories. Successfully discriminating brain patterns related to the processing of different valence cues via MVPA is of interest for two reasons. First of all, this would illustrate the ability of MVPA to disentangle closely overlapping neural substrates. This in turn would allow the detection of more fine-grained abnormalities that potentially underlie the dysfunctional emotion processing associated with depression. Furthermore, MVPA offers key

ingredients for successful fMRI neurofeedback (Sitaram et al., 2011): detection, decoding and prediction of neural states in a *short* period of time. Rapidly identifying activation patterns corresponding to specific tasks or states, instead of just focusing on single regions, might lead to more accurate neurofeedback and eventually boost its quality and long-term effects in depression, which is an area of current development (Linden et al., 2012).

To preempt our results, we show a successful application of MVPA in discriminating positive, negative and neutral valence cues in patients with depression. In addition, we demonstrate that less sensitive univariate approaches leave areas undetected that are highly discriminatory in MVPA. Finally, it was possible in our sample to discriminate healthy from depressed individuals based on differences in bivariate response patterns to stimuli of different valence.

8.3 Methods

8.3.1 Data

Nine patients (8 male; age range = 21-67 years, mean age = 48.8 years) suffering from unipolar depression as established by the SCID (First, Spitzer, Gibbon, & Williams, 2002) were included in the analysis (Table 8.1). None of the patients had any DSM-IV defined comorbidities. All patients were on anti-depressants, the dose of which remained stable for at least the six weeks preceding the intervention and for the entire duration of the study. Data was acquired on a 3-T Philips Achieva System (Best, The Netherlands) and data acquisition procedures were similar as in (Johnston et al., 2011; TR = 2 s, TE = 30 ms, 30 slices, 3-mm slice thickness, inplane resolution 2x2 mm). The same localiser as previously described in (Johnston et al., 2010; Johnston et al., 2011) was adopted, consisting of positive, negative and neutral stimuli adopted from the IAPS. IAPS pictures were employed as these induce the expressive, somatic and autonomic changes that are typically associated with affective expression, in a controlled manner (Lang et al., 1997). Additionally, the IAPS picture set

comes along with well-documented ratings of arousal and valence as these two factors have been found to explain most of the variance in evaluative judgments (Lang et al., 1997). During the localiser, 12 trials of each valence type (positive, negative and neutral) were presented in a pseudo-randomised order (Figure 8.1). Per trial either four neutral, negative or positive IAPS pictures were shown for 1.5 s each, alternating with a fixation baseline of 12 s. Two patients participated in three sessions during which they viewed the same localiser and the remaining patients in four sessions. Per patient we thus obtained a total of either 36 of 48 trials per valence condition. The functional data were preprocessed using motion correction and linear detrending to remove signal drift (GLM-Fourier, 2 sines/cosines). The data were then coregistered with the anatomical data and transformed into Talairach Space (Talairach & Tournoux, 1988).

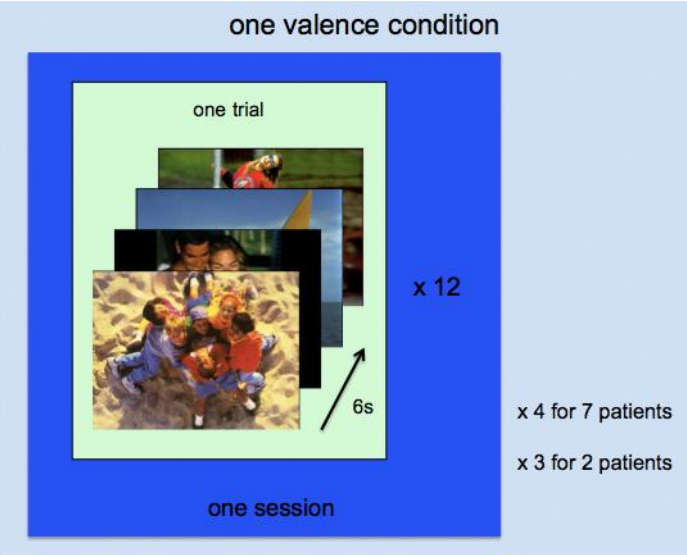

Figure 8.1. Schematic overview of data compiling one valence condition. Within one trial, four pictures of the same valence type (either positive, negative or neutral) were presented for 1.5 s each. Twelve trials were presented in each localiser session for each valence type amounting to either 36 or 48 trials per valence type per patient (depending on whether the patient had participated in three or four localiser sessions). A total of 144 (or 108) trials was obtained per patient collapsed over the three valence conditions and the four (or three) localiser sessions.

8.3.2 Multi-voxel pattern analysis

Trial estimation/ feature extraction

The BrainVoyager QX (Brain Innovation, Maastricht, The Netherlands) software was used to perform supervised multivariate pattern classification via the SVM. A general linear model (GLM) analysis was performed that computed voxel-wise beta estimates for each trial within each valence condition within the following contrasts: positive - negative, positive - neutral and neutral – negative. In total we thus obtained 48 sets of beta estimates per valence condition across all localiser sessions with the exception of two participants who only participated in three localiser sessions (total of 36 beta estimates per valence condition. The GLM predictors were created based on the timing of the block presentations of each stimulus valence type and were convolved with a haemodynamic response function. Additionally a predictor accounting for linear trend was added. No temporal or spatial smoothing was applied to ensure that the selection of informative voxels (and as a consequence the input for the classifier) was not biased as smoothing can hinder the detection of isolated voxels and can instead favour spatially clustered ones. The patterns of estimated beta values (*z*-normalised) were stored in feature vectors and served as input for the feature selection step.

Patient	Age (y)	Gender	HDRS-17	Medication (daily doses)
1	54	m	18	Iofepramine 140 mg, mirtazapine 30 mg
2	67	m	10	Amitriptyline 75 mg
3	37	m	21	Tranylcypromin 40 mg, lithium 400 mg
4	21	m	12	Fluoxetine 40 mg
5	44	m	21	Mirtazapine 30 mg
6	56	m	9	Sertraline 200 mg, reboxetine 8 mg
7	47	m	12	Citalopram 60 mg, quetiapin 100 mg
8	52	f	18	Citalopram 60 mg
9	61	m	12	Fluoxetine 20 mg

Table 8.1. Patient demographics.

Feature selection

Feature selection on the dataset is an essential step for the classification of fMRI data (see Mitchell et al., 2004; Norman et al., 2006) for background). The selected parameters are similar to (Yuen et al., 2012). The visual cortex was

masked by excluding all brain tissue posterior to the occipito-parietal sulcus to prevent categorization driven by differences in visual cortex responses to the dissimilar visual input in each condition. In addition, the ventricles were masked for each patient individually. An initial data reduction step via univariate F-tests followed by multivariate recursive feature elimination (RFE) has been found to result in maximum sensitivity and generalization performance (De Martino et al., 2008). First a crude selection was made by selecting the top 50% (13 000-27 000) of the voxels that showed the strongest activation, for each of the three contrasts (positive - negative, positive - neutral and neutral – negative). Then a more fine-tuned selection procedure was adopted that selected the top 5% (600-1400 voxels) of the remaining voxels via RFE. RFE gradually discards features until the voxels with the highest discriminative power remain (De Martino et al., 2008). We applied RFE via multiple cross-validation levels in which the training data were separated 10 fold and RFE was iterated 10 times. The input for every new iteration step was based on the remaining features of the previous iteration. At the end of this stage only the SVM weights of the selected voxels were retained for each trial. Five randomly selected trials out of 48 (or 36) were set apart as testing dataset while the remainder of the trials (either 43 or 31) served as training input.

Classifier training

In the third step a linear SVM, known for their good generalisation performance even in studies with relatively small datasets, was trained (see Belousov, Verzakov, & von Frese, 2002; Misaki, Kim, Bandettini, & Kriegeskorte, 2010 for background). A cross-validation procedure testing a series of different SVMs using different values for the regularization parameter C was run for each of the three contrasts separately (Cherkassky & Ma, 2004; Friedrichs & Igel, 2005). The data were split in 10 folds and one after another each dataset fulfilled the role of test dataset and the remainder of the data was used as training dataset. After N folds the average accuracy score was calculated and a slightly incremented C-value was tested. The C-value that resulted in the maximum cross-validation accuracy (and thus maximised the distance from the decision boundary (or hyperplane) to the closest data points

of the two valence conditions) was selected for the final (i.e. trained) SVM. This selected C-value maximised the distance from the hyperplane to the closest training data points of the two valence conditions. Each of these training data points represented a vector that contained the beta estimates of the selected voxels as computed during a trial. Since the exact location of the hyperplane depends solely on the data points closest to it, these data points are called support vectors, explaining the origin of the name support vector machines. The C-value, which establishes the trade-off between classification accuracy and generalisability, that resulted in the maximum cross-validation accuracy determined the optimal hyperplane that separated the training trials of the valence conditions. This hyperplane, or decision boundary, can be described by the linear discriminant function $f(x) = wx + b$, where w is the vector containing the SVM weights, x the training patterns containing the beta estimates of the valence conditions in the contrast (of the selected voxels) and b the bias term. Depending on the side of the decision boundary at which the training pattern of a trial appeared in feature space, a trial was assigned to one of the two valence conditions in the contrast. The class assignment was then checked with the experimental protocol to determine the correctness of the classification. In the last phase of this third step an overall accuracy score indicating the proportion of correctly allocated training trials was calculated for each contrast separately.

Classifier testing

In the final step of the MVPA the remaining data served as input for the trained SVM to test the performance on a set of input new to the classifier. This SVM was used to predict the categories of the test trials for each contrast and individual separately. Overall prediction accuracy scores for each contrast were computed based on the prediction accuracy of all trials together. For all contrasts five trials (out of 48/36 trials) of each condition were randomly selected to be left out of the training stage (decoding and classifying) which later served as testing (predicting) data.

Group-level activation probability maps

Group-level probability maps were generated to determine the areas that were driving the classifications. For this purpose, individual discriminative maps based on the SVM weights were created first for each of the three contrasts. These served as the basis for masks that contained all discriminative voxels. Group-level probability maps were then calculated via these masks and were smoothed with a 4 mm FWHM Gaussian kernel to adjust for individual differences in neural anatomy. These maps were thresholded at 60%, entailing that a voxel only appeared on the probability map if it was discriminative in more than five individuals.

Permutation tests

Finally permutation tests were performed to compare the performance of the classifier to a null-distribution. The trials were randomly categorised after which the classifier was retrained with these new and possibly wrong categorisations. This classifier was repeatedly tested (200 permutations) with a 'leave one out' cross-validation method and provided a null distribution that showed the probability of gaining a correct classification result while the conditions were randomly allocated. Classification accuracies of above the 95^{th} percentile of the null distribution indicated that a significant classifier accuracy result was obtained.

8.3.3 Univariate analysis

The sensitivity of the multivariate method was compared with a univariate analysis. In accordance with standard univariate analysis procedures the data were corrected for head motion, linearly detrended and temporally (3 sec) and spatially smoothed (4 mm FWHM Gaussian Kernel) to increase the signal-to-noise ratio for the group analysis. The same mask as in the multivariate method was applied for each patient. A conventional single-subject GLM ($p < .05$) was performed for the three contrasts. This served as the basis for individual masks of the activated voxels in each valence condition in each contrast. Group-level activation probability maps (thresholded at 60%) were generated based on these masks to allow for comparison with the multivariate probability maps.

8.3.4 Group classification

In follow up of the MVPA results we investigated whether it was possible to discriminate activation patterns in response to different valence conditions in different groups of people. Due to software limitations this was not examined via MVPA but a bivariate differentiation analysis similar to (Ihssen, Cox, Wiggett, Fadardi, & Linden, 2011). Since the healthy controls only participated in 12 trials it was not possible to train a separate classifier on the data collected in healthy controls either. Instead, the localiser data of one session of nine healthy controls (7 male, age range = 30-56 years; mean age = 38 years) were added to the localiser dataset of the first session of the depressed patients. The data had been collected during a previous study (Johnston et al., 2010) that applied the same localiser protocol as the depression study. There was no significant difference of age between the two groups ($t(16) = 2.023$, $p > .05$) and both groups were matched for gender. Activity maps were created via a two-way ANOVA to identify areas that showed a significant interaction between group and valence contrast. As this was an exploratory analysis an arbitrary threshold of $p < .002$ was chosen that would ensure that only the most discriminative areas would be maintained in the analysis. Subsequently two stepwise linear discriminant analyses (LDAs) were conducted in SPSS 18.0 (SPSS, Chicago, IL, USA) that searched for the brain areas with the highest discriminative power and thereby investigated how well the different areas discriminate between the healthy and depressed group. One LDA was conducted with all areas identified on the activity maps and another with all areas that survived multiple comparison correction via cluster thresholding ($p < .05$, cluster size threshold of 108 mm^3 for all three valence contrasts). After this exploratory analysis another stepwise LDA was conducted that is not affected by a potential bias from circularity. For each of the three valence pairs the five clusters that showed the most significant main effect of valence were identified. From these 15 areas the clusters surviving cluster threshold correction ($p < .05$, cluster size threshold of 108 mm^3 for the contrast [positive – negative], 81 mm^3 for the contrast [positive – neutral] and 135 mm^3 for the contrast [neutral – negative]) were selected as input for the LDA. Areas that also showed a

significant interaction between group and valence contrast were excluded from the LDA. The generalisation of the classifier was tested via a leave-one-out cross-validation procedure.

8.4 Results

8.4.1 Multi-voxel pattern analysis

For all valence discriminations the SVM achieved accuracy levels between 80 and 100% (positive - negative: 92%; negative - neutral: 86%; neutral - positive 89%). The permutation tests demonstrated the statistical significance of the SVM accuracy results as the obtained discrimination accuracy for all valence labels and all depressed subjects was significantly higher than at the chance level of .05 (Figure 8.2).

The emotional valence information for neutral, negative and positive stimuli in depressed patients was reflected in a highly distributed activity pattern across the brain and covered areas that have previously been linked to emotional processing (see Appendix for table with complete overview). Several areas were identified that are part of the fronto-limbic system such as the VLPFC, insula, striatum, cingulate cortex, amygdala and hippocampus (Figure 8.3). None of these areas showed selectivity for only one valence condition (Table 8.2). Instead they contained voxels weighted for several valence conditions in several contrasts, albeit at varying locations within that area.

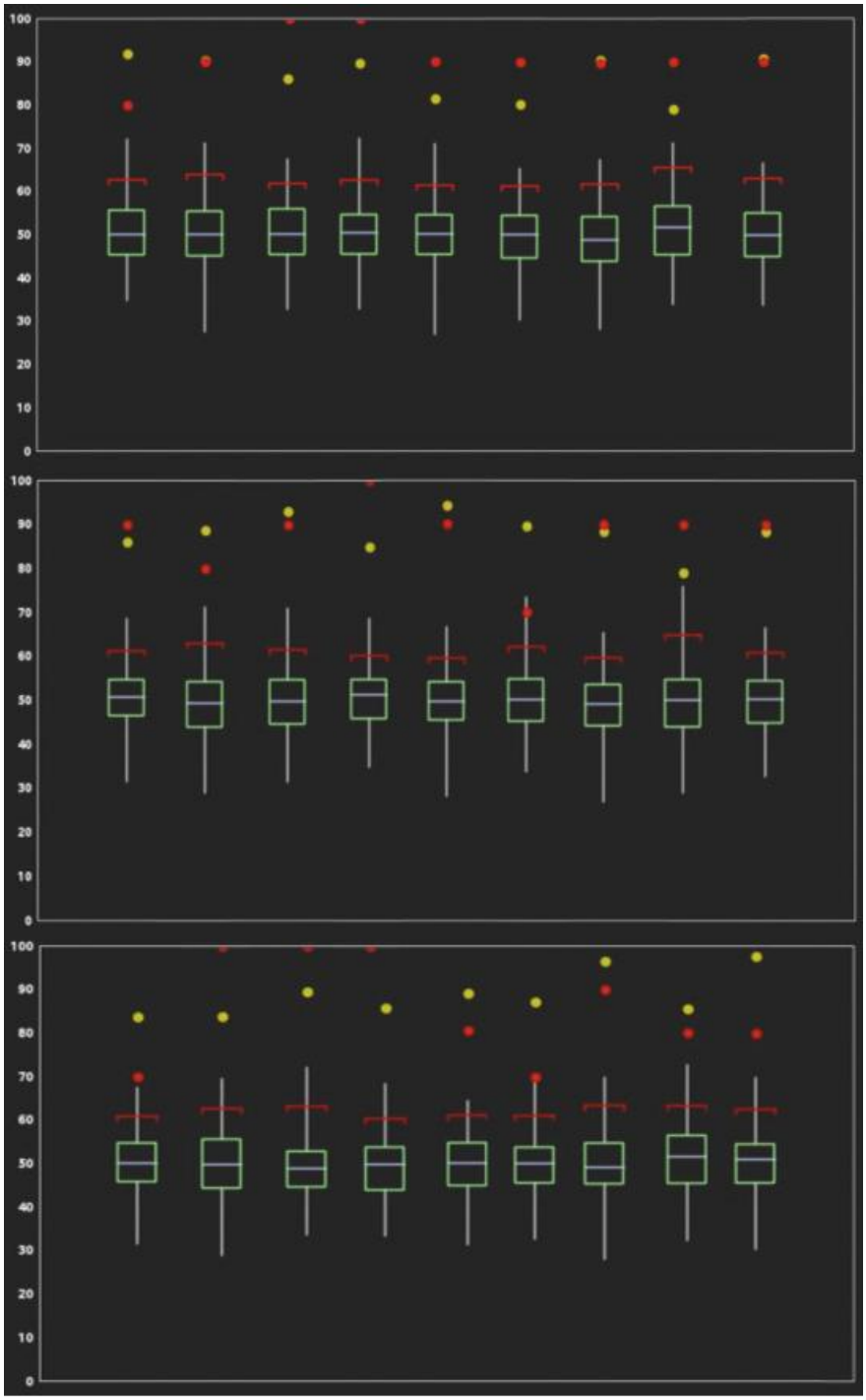

Figure 8.2. Permutation plots indicating statistical significance of SVM classifier. The permutation plots show the accuracy obtained with a classification based on the test data (red disk) or training data (yellow disk), in comparison with a null-distribution. The top panel shows the permutation plots obtained for the contrast positive versus negative, the middle panel for the contrast positive versus neutral and the bottom panel for the contrast neutral versus negative. The red line indicates the 95% threshold.

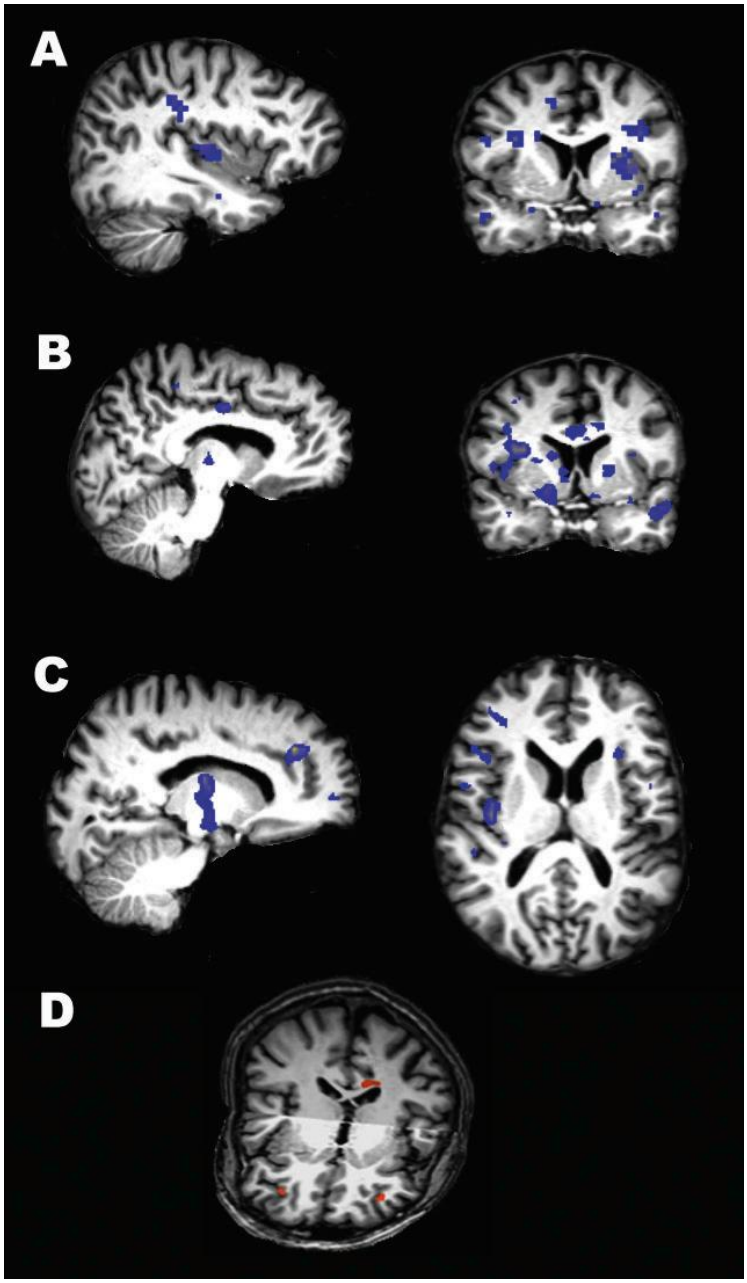

Figure 8.3. Areas underlying the valence patterns for the three different contrasts as identified via MVPA. A) contrast positive versus negative. Areas carrying information about positive valence included the insula, parahippocampal gyrus and postcentral gyrus (x = − 37). For negative valence the areas included the putamen, inferior frontal gyrus (IFG), middle frontal gyrus (MFG), middle temporal gyrus (MTG), parahippocampal gyrus, ventral striatum and cingulate gyrus (y = 4, radiological convention). The areas that form part of the valence patterns are coloured in blue. B) Contrast positive versus neutral. The cingulate gyrus and hypothalamus were amongst other regions part of the pattern underlying positive valence (x = − 9). The cingulate gyrus, insula, putamen, superior temporal gyrus (STG) and occipitotemporal gyrus (OTG) formed part of the pattern underlying neutral valence (y = 4, radiological convention). C) Contrast neutral versus negative. For neutral valence the anterior cingulate gyrus (ACG), thalamus and midbrain carried information related to neutral valence (x = 15). For negative valence the areas included the orbitofrontal cortex (OFC), IFG, temporoparietal junction (TPJ) and insula (z = 12, radiological convention). D) Differential activation patterns in the depressed and healthy group, in the contrast positive versus negative, were found in the bilateral ventrolateral cortex (VLPFC) and dorsal cingulate gyrus (all represented in orange) and allowed group classification with an accuracy of 100%.

	Positive vs Negative		**Positive vs Neutral**		**Neutral vs Negative**	
	Pos	*Neg*	*Pos*	*Neu*	*Neu*	*Neg*
Insula	x	x	x	x	x	x
IFG	x	x	x	x	x	x
Amygdala		x	x			x
Caudate nucleus	x			x	x	
Putamen	x	x	x	x	x	
Hippocampus	x	x	x	x	x	
ACG		x		x	x	

Table 8.2. Fronto- limbic areas aiding classification per valence condition per contrast. IFG = inferior frontal gyrus, ACG = anterior cingulate gyrus.

8.4.2 Univariate analysis

The group-level activation probability maps across all patients created by univariate analysis were thresholded at the same level (60%) as in the multivariate approach. Only activation related to negative valence survived this threshold. For positive valence, the first activation appeared at 50% (contrasted to the neutral condition) and at 40% (contrasted with the negative condition).

8.4.3 Group classification

An LDA was performed to investigate the differentiability between affect processing areas in depressed and healthy participants. Exploratory activation maps were constructed for the interaction 'group' x 'valence contrast' to identify areas that would serve as input for the LDA (Table 8.3A). Based on the activation levels in four areas, the stepwise LDA was able to correctly classify all participants. These areas were the right VLPFC and dorsal cingulate gyrus in the [neutral – negative] contrast, the left VLPFC in the contrast [positive – neutral] and the dorsal cingulate gyrus in the contrast [positive – negative]. For both areas located on the cingulate gyrus the depressed group had higher activation levels in the negative than neutral or positive conditions, whereas the healthy controls had lower activation levels in the negative than neutral or positive conditions (Figure 8.4A). When the LDA was conducted with the areas that had survived cluster threshold correction (Table 8.3B), the cluster in the right VLPFC in the contrast [neutral – negative] was retained and was able to

classify all individuals with 100% accuracy in conjunction with a cluster in the MFG and IPL in the contrast [positive – neutral] (Figure 8.4B).

The stepwise LDA based on only areas showing a main effect of valence (Table 8.4) correctly classified all participants based on activation levels in the caudate nucleus and dorsomedial prefrontal cortex (DMPFC; Figure 8.4C). In the cross-validation procedure that was run to test the generalisation of the classifier, 72.2% (chance level: 50%) of all cases were correctly classified as either belonging to the depressed or healthy group.

To summarise, the SVM classified the different valence conditions in patients with depression with high accuracy. Several of the neural correlates underlying these conditions form part of a fronto-limbic system. Conversely, a standard univariate analysis did not pick up any activation differences with the same sensitivity. Based on the activity patterns in the DMPFC and caudate nucleus the LDA was able to perfectly separate healthy from depressed individuals.

A. Group x valence contrast interaction (p < .002)			
Region	Side	TAL coordinates	NrOfVoxels
1. Group x (positive-negative) interaction			
Dorsal cingulate gyrus	**L**	**-13 / -21 / 29**	**326**
Amygdala	R	23 / 4 / -18	4
VLPFC	R	27 / 41 / 0	31
	L	-31 / 43 / 1	99
Precentral gyrus	**R**	**24 / -7 / 48**	**348**
2. Group x (positive-neutral) interaction			
MFG	**L**	**-41 / 4 / 50**	**139**
VLPFC	L	-55 / 6 / 20	60
Postcentral gyrus	**R**	**42 / -28 / 44**	**229**
	L	-30 / -20 / 42	56
Subgyral region	L	-37 / -32 / 0	12
SFG	L	-19 / 36 / 45	34
IPL	**L**	**-39 / -39 / 37**	**151**
	L	**-47 / -33 / 39**	**342**
DMPFC	L	-12 / 34 / 42	20
Insula	L	-40 / -8 / -9	4
3. Group x (neutral-negative) interaction			
VLPFC	**R**	**33 / 41 / 0**	**225**
	L	-34 / 38 / -2	108
DMPFC	R	10 / 44 / 37	81
Caudate nucleus	L	-15 / -3 / 20	58
Precuneus	R	15 / -54 / 38	66
	L	-17 / -62 / 30	57
Dorsal cingulate gyrus	L	-13 / 13 / 27	6
Precentral gyrus	R	51 / -16 / 47	24
IPL	R	28 / -53 / 27	13
Posterior cingulate gyrus	R	17 / -42 / 9	12

Table 8.3. Areas selected as LDA input. The areas surviving cluster threshold correction are printed in bold. VLPFC = ventrolateral prefrontal cortex, MFG = middle frontal gyrus, SFG = superior frontal gyrus, IPL = intraparietal lobule, DMPFC = dorsal medial prefrontal cortex, MTG = middle temporal gyrus, STS = superior temporal sulcus, ITS = inferior temporal sulcus.

B. Main effect valence per contrast (p < .001)			
Region	Side	TAL coordinates	NrOfVoxels
1. Contrast (positive-negative)			
MFG	**R**	**42 / 15 / 30**	**352**
DMPFC	**L**	**-4 / 43 / 46**	**424**
MTG	**L**	**-57 / -20 / -6**	**253**
VLPFC	**R**	**35 / 23 / 19**	**141**
Insula	L	-33 / 3 / 10	60
2. Contrast (positive-neutral)			
DMPFC	**R**	**3 / 24 / 45**	**11**
MFG	R	41 / 19 / 31	227
Putamen	R	32 / -10 / 13	56
Midbrain	R	19 / -17 / -9	22
Insula	L	-33 / -23 / 15	19
3. Contrast (neutral-negative)			
Caudate nucleus	**L**	**-11 / 5 / 14**	**224**
STS	L	-38 / -52 / 9	87
VLPFC	**L**	**-30 / 27 / 4**	**254**
MTG	**L**	**-42 / -70 / -5**	**772**
ITS	**R**	**39 / -61 / -11**	**515**

Table 8.4. Continued.

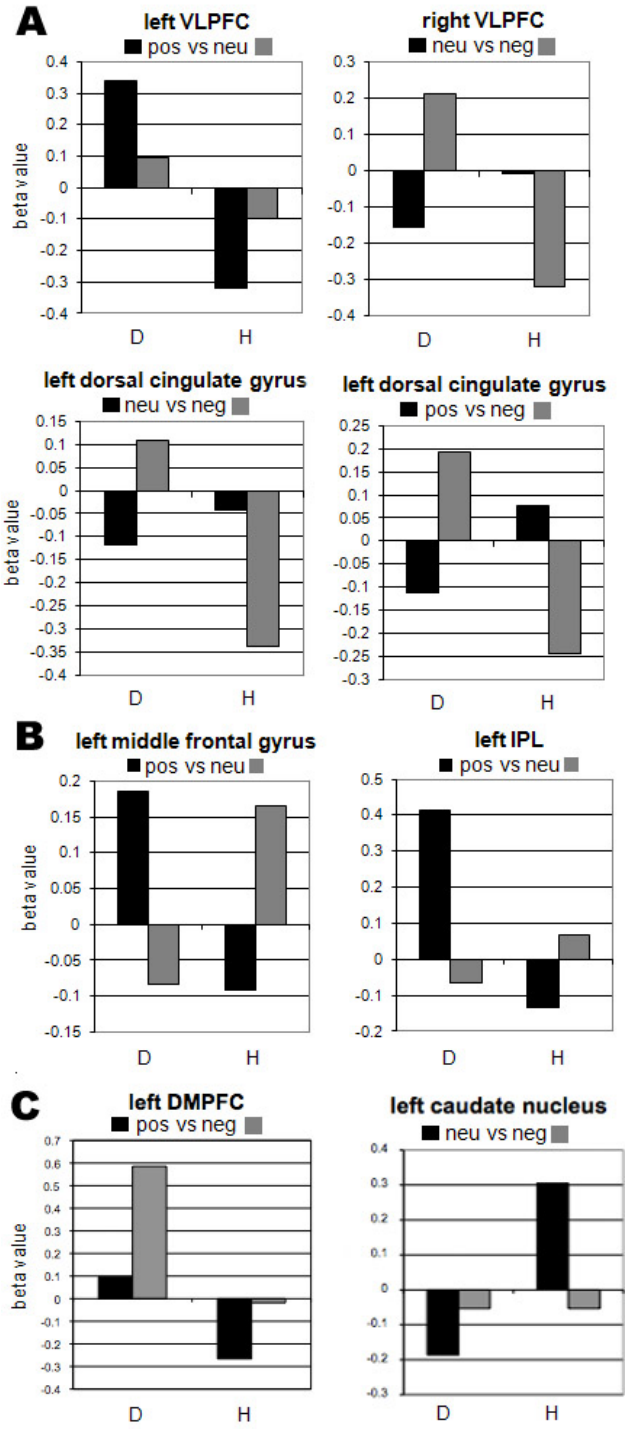

Figure 8.4. Activation patterns of the areas underlying successful group classification. A) Areas identified via a 'group' × 'valence contrast' interaction, without cluster threshold correction. Based on the bivariate response patterns in four areas (in different contrasts) all participants were classified in the correct group. Elevated activation levels were found for negative valence in the depressed group in comparison to the healthy control group. B) Areas identified via a 'group' × 'valence contrast' interaction, surviving cluster threshold correction. The bivariate response patterns of three areas that survived cluster threshold correction allowed successful group classification. Apart from a cluster in the right VLPFC that was identified without cluster threshold correction, the left MFG and left IPL showed a marked difference in the activation pattern in both groups. C) Areas identified via a main effect of valence, surviving cluster threshold correction. The group classification was based on the bivariate response patterns in the left DMPFC and left caudate nucleus. D = depressed, H = healthy.

	Input based on areas showing a 'group' x 'valence contrast' interaction			
	Wilks λ	**χ^2**	**Significance level**	**Classification accuracy**
All contrasts before cluster threshold correction • VLPFC *(neu-neg)* • VLPFC *(pos-neu)* • Dorsal cingulate gyrus *(neu-neg)* • Dorsal cingulate gyrus *(pos-neg)*	0.067	37.067	p < 0.001	100%
All contrasts after cluster threshold correction • MFG *(pos-neu)* • IPL *(pos-neu)* • VLPFC *(neu-neg)*	0.159	26.768	p < 0.001	100%
	Input based on areas showing a main effect of valence			
	Wilks λ	**χ^2**	**Significance level**	**Classification accuracy**
All contrasts after cluster threshold correction • Caudate nucleus *(neu-neg)* • DMPFC (*pos-neg)*	0.477	11.094	p = 0.004	100%

Table 8.5. Stepwise LDA results. VLPFC = ventrolateral prefrontal cortex, MFG = middle frontal gyrus, IPL = intraparietal lobule, DMPFC = dorsomedial prefrontal cortex.

8.5 Discussion

8.5.1 MVPA findings

This study identified activation patterns of specific valence conditions elicited by IAPS pictures in patients with unipolar depression. The group-level probability maps obtained via MVPA showed that a distributed pattern of brain regions contributed to the representation of each valence condition, with overlap in the brain areas associated with the different valence conditions. The

overlap could indicate that an area fulfills a more general role in affective processing such as emotion reappraisal (Ochsner & Gross, 2005) or may indicate emotion specific involvement in both valence conditions, for example arousal responses that are similar across valence directions. Our findings in patients are thus generally in line with previous studies in healthy individuals (Baucom et al., 2012; Johnston et al., 2010; Murphy et al., 2003; Yoon et al., 2008; Yuen et al., 2012) and confirm the view that neural correlates of affective states are dispersed across the brain. Anderson and Oates (2010) have criticised the identification of neural correlates via MVPA arguing that MVPA can yield unstable results. However, Li et al. (2012) demonstrate the effectiveness of recursive feature elimination in combination with permutation tests to improve the overlap between informative features obtained in different folds and to limit the chance of including irrelevant features. If the MVPA results had indeed been unstable like Anderson and Oates argue then the likelihood of measuring substantial overlap of discriminative voxels across participants, as shown on the group-level probability maps, would have been slim. We thus argue that our RFE approach allowed us to obtain discriminative voxels that were indeed informative in different individuals. This approach alone does not refute the other main critique brought forward by Anderson & Oates, that successful classifier performance does not imply that the brain solves a task in the same way. Although we did not address this issue by testing performance of different classifiers, we are confident that the identified brain areas contributed to the perceptual-affective response to emotional valence because several of the discriminatory areas identified in the current study form part of a fronto-limbic system of areas involved in emotion processing and/or are dysfunctional in patients with depression (Damasio, 1998; Drevets, 2001; Phan et al., 2002; Phillips et al., 2003b), including the insula, amygdala, striatum, thalamus, hippocampus, SFG, (anterior) cingulate cortex and VLPFC.

Our study explored the neural underpinnings of the processing of IAPS pictures in a depressed sample via multivariate analysis. Several other studies have previously investigated the discriminability of different types of valence via a multivariate approach in healthy individuals (e.g. Sitaram et al., 2011; Baucom et al., 2012; Yuen et al., 2012) or patients with mood disorders (e.g. Mourão-

Miranda, Almeida, et al., 2012). The classifier accuracies that we obtained are comparable with similar studies. Baucom et al. (2012) presented IAPS pictures of different levels of arousal and valence to healthy participants and achieved accuracy scores around 80%. One explanation for the high classification accuracies in their study may be that the physical properties of the visual stimuli were more similar within than across valence conditions. Although they matched the stimuli set for hue, saturation and intensity values, identical stimuli could be repeated in the training and test trials, and the same was true for our study. To prevent the low level visual properties of the stimulus set from interfering with the classification of the emotional content we therefore excluded the posterior cortex from the analysis. Mourão-Miranda, Almeida et al. (2012) trained a classifier to discriminate between happy and neutral faces presented to groups composed of healthy controls, unipolar depressed patients and bipolar patients. Prediction rates of 81%, 70% and 61% respectively were obtained. In our study we show that high classification accuracies can be obtained even when comparing positive or negative emotions with a neutral condition in patients with unipolar depression.

Our study also shows that high classification accuracies can be obtained across sessions, which attests to the good reliability of the procedure. The stable representation of valence across the brain and across time is relevant for further clinical applications such as fMRI neurofeedback. Future neurofeedback studies will have the option to provide feedback of brain patterns (LaConte, 2011; Shibata et al., 2011; Sitaram et al., 2011) instead of restricted regions-of-interest (ROIs) which might lead to more pronounced behavioural effects. As an example, the design of this study could be translated into a neurofeedback paradigm in which depressed patients would receive neurofeedback on their emotion regulation in response to the presentation of the positive, negative or neutral IAPS pictures. As depression has been associated with physiological abnormalities that are dispersed across the brain, it might be crucial to attempt to regulate patterns of brain activity across the whole brain with the aid of MVPA. Given the time constrains that apply to neurofeedback, the feasibility of real-time feedback from a pattern classifier was tested by running the SVM procedure only once. This resulted in very high prediction accuracies

suggesting that the future for neurofeedback experiments applying real-time classification looks promising.

8.5.2 Univariate versus multivariate analysis

Although the sensitivity threshold of the univariate and multivariate analysis seem to differ only marginally, the group-level probability maps resulting from the univariate analyses were based on a substantially higher number of voxels due to the feature elimination steps conducted in the multivariate analyses. While the masks used to create the univariate-based group maps contained on average 109701 voxels, the number of voxels that survived RFE ranged from 600 to 1400. Hence the likelihood of spatial overlap between discriminative voxels was much higher in the univariate compared to the multivariate analysis. Yet, we found the opposite: the group-level probability maps based on the univariate analysis showed less spatial overlap than the multivariate-based group maps. Because of the ability of MVPA to detect fine-grained activation patterns, MVPA thus seems more sensitive to detect stable representations. One reason for the lower stability of the univariate analysis might be that the activity levels in the areas for different conditions cancel each other out because of the high overlap between the conditions (Murphy et al., 2003). Another explanation could be that relatively weak activations that discriminated between conditions are too subtle to be picked up by univariate approaches. Several studies that compared the neural correlates of different valence conditions via a passive IAPS picture viewing paradigm in healthy subjects did find suprathreshold clusters. A direct comparison of negative over positive valence for instance resulted in clusters in the bilateral VLPFC and along the left middle and bilateral superior temporal gyrus in one study (Kensinger & Schacter, 2006), yet did not result in any significant clusters in another (Gerdes et al., 2010). It must be noted however that different studies selected different pictures from the IAPS database and that these studies were conducted in healthy individuals.

8.5.3 Group classification findings

Although we cannot make any claims about the predictive performance of the LDA analysis as it was based on activity maps created from the same data, our

results suggest that significant differences exist between healthy and depressed individuals with respect to valence processing. The exploratory LDAs demonstrated that based on clusters in the bilateral VLPFC and dorsal cingulate cortex a perfect separation between the data of depressed patients and healthy controls was obtained. One previous classification study investigated which mixture of task conditions resulted in the maximum discrimination between healthy and depressed individuals (Hahn et al., 2011). While the single level classifiers performed above chance when taking neutral, happy or sad faces into account, it was only the responsiveness to neutral faces that served as a vital discriminatory criterion. It thus seemed that the differences between patients and controls in response to viewing happy and sad faces were highly similar to those in response to neutral faces. In contrast, the results from the current study suggest that the responsiveness to all valence levels was distinct in healthy and depressed participants. A potential explanation for the discrepancy in results is that our study used broader emotion categories because of which there were more facets along which healthy and depressed individuals could have differed, thereby being more suitable for group classification purposes. An alternative reason might be that in order to identify the most discriminative classifier, Hahn et al. (2011) predicted the accuracy for each of the 15 single condition classifiers as well as a decision tree algorithm that combined the descriptive probabilities of all single classifiers first. It has been demonstrated that the testing and selection of (most relevant) dependent variables from a subset inflates false-positive results (Simmons, Nelson, & Simonsohn, 2011) yet the study did not take any measure to correct for potential type I errors. Its findings should thus be interpreted with caution. In contrast to Hahn et al. we obtained high group classification accuracies while solely depending on the neural patterns underlying emotion processing. This is intriguing since symptom constellations can vary considerably across patients with depression. Nevertheless our results suggest some common ground in emotion processing across patients with depression. We have also provided preliminary evidence that this neural basis differs from that observed in healthy controls. The replication of successful classifiers with independent samples could contribute to the development of biomarkers of mood state that might be used in the diagnosis and longitudinal monitoring of mood disorders.

8.5.4 Limitations and future studies

The major limitation of this study is that the datasets were not optimally designed for classification purposes. Consequently the test data in the MVPA was not comprised of an independent sample. In addition, any medication-related differences cannot be ruled out due to the nature of both groups. Another limitation is that even though the visual cortex was excluded in the classification and prediction processes it cannot be ruled out that neural responses to the identical physical features of the stimuli in each session may have aided classification. The limited number of trials acquired in our healthy sample unfortunately did not allow a comparison of MVPA results obtained in healthy and depressed participants. Even though this was not the aim of our paper, which was to investigate the feasibility of pattern classification of valence in a depressed sample, future studies should attempt to contrast healthy and depressed individuals via MVPA. This may reveal potential differences previously unidentified by univariate methods. It would be beneficial for future studies to adopt larger datasets since the small number of participants in the current study limits the generalisability of our findings. Finally, future studies are required to confirm the advantage of multivariate over univariate analysis in other forms of emotion processing and other domains.

8.5.5 Conclusion

In conclusion, this study illustrated the capacity of multivariate analysis of brain activation data to successfully differentiate between highly overlapping neural activations that carry information about emotional valence in patients with depression with a limited numbers of trials and its superior sensitivity compared to the univariate analysis conducted in this study. Moreover, it appears that in our sample depressed patients could be separated from healthy controls with the use of regional activity patterns and the appropriate valence contrast. However, we did not test the discriminatory power of the same patterns in an independent patient group, which would be necessary to infer valid classification in the general population. The long-term goal of this research programme is the development of reliable diagnostic markers that

allow the discrimination between healthy and depressed individuals, the identification of current mood state and predictions of which individuals are most likely to benefit from certain type of treatments (Mourão-Miranda, Oliveira, et al., 2012).

Chapter 9 - General discussion

9.1 Summary and interpretation of findings

The work described in this thesis investigated the potential of functional magnetic resonance imaging (fMRI)-based neurofeedback as a treatment tool for depression. This was of interest for several reasons. First of all, a substantial amount of depressed patients does not respond satisfactorily to currently existing treatments for this debilitating mental disorder (Rush et al., 2006). Secondly, this technique makes it possible to target both the biological and cognitive component of depression in a non-invasive and individualised way. To understand the true clinical value of a course of neurofeedback training in depression, it is necessary to assess its impact on depression severity. These measures were obtained in the study described in Chapter 5 but were not analysed as the dataset used in this thesis is part of an ongoing clinical trial for which new data is still being collected.

In investigating the worth of neurofeedback as an add-on treatment for depression, the inclusion of an adequately designed control group is critical (Sulzer, Haller, et al., 2013). Chapter 4 therefore investigated the feasibility of a particular type of control group which may be most suitable for neurofeedback studies involving mood disorders. The overall experience of patients assigned to the control group was namely as similar as possible to patients in the experimental group, with the only difference being that the former received neurofeedback from the parahippocampal place area (PPA) and the latter from an emotion processing area. The control group thereby controls for patient-researcher contact, environmental setting, expectancy effects and (rewarding) effects of the acquisition of self-regulation ability. The findings of Chapter 4 suggested that healthy volunteers can learn to up-regulate PPA activation in a localised manner and that no behavioural changes resulted from this, thereby confirming the suitability of this particular control group for the depression study. A potential challenge created by this control group however is that it

might not be straightforward to deduce any conclusions from the full dataset with regard to the effectiveness of neurofeedback from emotion areas in alleviating symptoms of depression. As it is likely that both the patients in the EMO and PPA group acquired an enhanced sense of self-efficacy of thought control, it can be expected that both groups will show a reduction in depression severity. It is hypothesised that this reduction will be larger in the EMO than PPA group due to additional benefits of the targeted biological substrate. But even though neurofeedback allows a more direct investigation of brain-behaviour relationships than more traditional research methods, caution is required when identifying the cause of any additional clinical improvements in the EMO group. The main reason for this caution is that because patients engaged in recollecting happy memories to up-regulate positive emotion areas, it cannot be established whether any improvements in mood occurred due to reliving these memories or due to heightened brain activation in these areas instead. However, the control group in the pilot study showed that positive emotion imagery does not have a long term improving effect on mood state (Linden et al., 2012). This case illustrates the difficulties associated with control group selection and the possible advantage of the inclusion of a combination of control groups. In essence, the design of the control group depends heavily on the task at hand and whether it needs to establish for example the necessity of the feedback signal for acquiring self-regulation abilities or benefits of neurofeedback over repeated training with appropriate task instructions but without feedback. Therefore, no single control group is superior to all others.

The next few chapters then focused on the mechanisms via which neurofeedback could potentially alleviate depression, by assessing whether this method indeed affects neurobiological and cognitive pathways that have been established as key players in the formation and continuation of depression. Chapter 5 showed that although the target areas in both patient groups were selected based on externally generated input, while the voluntarily up-regulation had to be achieved via internally generated images, all patients in both groups managed to execute the self-regulation task successfully. In the current study it was chosen to train patients to heighten the activation in a

positive emotion processing area. In this approach patients had to use positive imagery to master this task, which introduced a cognitive pathway to targeting depression. At the same time, a wider network of emotion regulation areas was targeted due to the extensive interconnectivity in the brain (Chapter 6). Thus, although the selected approach may result in an activation increase in an emotion area that already shows hyperactivity in depression, this can still enforce areas to be subject to increased regulation after neurofeedback training. The selected target areas were often located in the prefrontal cortex, which is known to be involved in affective control and to have important functional connections with other emotion areas. Related to this, it has been found that up-regulation of the amygdala via positive emotion induction resulted in increased functional connectivity with various regions in the prefrontal cortex (Zotev et al., 2011). A similar mechanism may account for the significant main effect of *Group* found in the amygdala. Instead of training patients to up-regulate a positive emotion area, regardless of whether this area was hyper- or hypo-activated compared to healthy participants, another option would have been to train patients in the EMO group to restore the abnormal brain activation levels associated with depression. One example of this instance would be asking patients to lower the activation in an overactive limbic system component. This approach might be problematic because it is unknown whether a deviant activation pattern in any area is relatively directly related to the depression or is perhaps the consequence of that area trying to compensate for another area more directly affected by depression. In addition, no studies to date have investigated the feasibility of identifying and quantifying aberrant activation levels in individual patients.

The findings presented in Chapter 7 seem to support the notion that neurofeedback training can positively influence perceived self-efficacy of thought control, although it must be noted that a small sample size and multiple testing were used rendering the statistical outcome less reliable. Additional findings documented in this chapter suggested that neurofeedback is more suitable for some patients than others, as the neurofeedback training seemed to have less effect on patients with relatively more severe depression and less

perceived thought control ability at the start of the trial. This underlines the importance of early diagnosis of depression.

Lastly, Chapter 8 investigated the feasibility of adapting the neurofeedback paradigm employed in the current work to a procedure that more closely reflects the distributed information processing in the brain. Recent advances in technology make it possible to provide feedback from brain activation patterns underlying the task of interest (LaConte, 2011; Shibata et al., 2011; Sitaram et al., 2011). This is of considerable interest for neurofeedback paradigms targeting depression given the wide variety of brain areas identified as the neurobiological substrate of depression. The provision of feedback from, for instance, brain patterns underlying positive valence as identified via multi-voxel pattern analysis (MVPA), opposed to one delineated area, may therefore result in an increased clinical benefit of neurofeedback training. However, the brain patterns underlying the passive viewing of International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1999) pictures of different valence types in depression had not been investigated before. In addition, it was unknown whether these patterns can differentiate healthy from depressed individuals, which would open up the appealing option to provide depressed patients with feedback patterns of valence derived from healthy volunteers. The presented findings confirmed that valence-associated patterns are widely dispersed across the brain and indicated that there are significant differences between the valence patterns expressed in healthy and depressed individuals. The most notable differences were present in the ventrolateral prefrontal cortex (VLPFC) and dorsal cingulate cortex. Patterns involving these areas could be set as the target brain state which depressed patients have to attempt to match via self-regulation training, which may facilitate restoring normal brain functioning in depression.

A limitation of the current study is that the nature of the study design does not allow implementing the intervention in a double-blinded fashion. Nevertheless, it is unlikely that experimenter bias influences the clinical trial outcome. The only components that the experimenter has direct influence over are the selection of the target area and the thermometer sensitivity, which affected

reward rate. No group differences were found in target area size or in reward rate in the current subset.

It could be argued that as a consequence of the instructions provided to the patients in both groups, there may have been some overlap in the strategies adopted by both groups. Patients in the PPA group may have experienced some positive emotions as they may have regarded the relaxing environments as positive and patients in the EMO group may have been imagining tranquil places that they think of positively. Indeed, two patients in the EMO group did report thinking of sunny scenes or the house where the patient had grown up. Nevertheless, it can be expected that patients in the EMO group activated a wider network of emotion areas as for instance amygdala activation was only found in the EMO group.

9.2 Context

Although a wide variety of treatment methods for depression exist, these have been found insufficiently adequate to treat a substantial proportion of patients suffering from depression (Rush et al., 2006). While neurofeedback shares some components with currently existing treatment methods such as psychological and pharmacological treatment, it also offers some unique benefits. Nevertheless, only one study other than our pilot study (Linden et al., 2012) has investigated fMRI-based neurofeedback in depression. The results from that study cannot establish whether neurofeedback can alleviate symptoms of depression as only short-term mood changes were assessed (Young et al., 2014). Other drawbacks of this study are that group allocation was not randomised, that there was a significant difference in proportion of co-morbid diagnoses between the experimental and control group and that the study did not control for the amount of positive feedback provided to both groups.

Various other novel methods to alleviate symptoms of depression are currently being investigated as well. One example is transcranial magnetic stimulation (TMS), which has now received FDA approval for treatment-resistant

depression (George & Aston-Jones, 2010). However, mixed results have been published about the efficacy of TMS (Herrmann & Ebmeier, 2006; Rodriguez-Martin et al., 2001), it can be experienced as uncomfortable and the most commonly applied placebo condition does not match the sensation induced by actual TMS pulses. Nevertheless, TMS might have a positive effect on depression as well as on certain cognitive functions such as verbal fluency and working memory (Moreines, McClintock, & Holtzheimer, 2011). Some findings have suggested a positive effect of vagus nerve stimulation (VNS) on depression. This method requires the implantation of electrodes and a generator and is thus relatively invasive. However, improvements in depression have been found even long after its administration (Marangell et al., 2002). Another technique proposed to treat depression is transcranial direct current stimulation (tDCS), although the clinical benefits for depression have so far only been tested in pilot studies (Nitsche, Boggio, Fregni, & Pascual-Leone, 2009). These findings thus still have to be replicated in larger randomised controlled trials.

The aforementioned methods do not explicitly target the cognitive emotion regulation system related to depression. A recent study reported a noteworthy alternative to improve emotion regulation, namely via emotional working memory training (Schweizer, Grahn, Hampshire, Mobbs, & Dalgleish, 2013). The study found that the same frontoparietal circuit that was involved in the cognitive regulation of affect played a role in working memory tasks. The affective dual *n*-back task used by Schweizer et al. (2013) is less likely to target the cognitive emotion regulation system that can potentially ameliorate depression than neurofeedback training. Patients namely did not have to engage in the effortful regulation of their mood but instead had to identify whether the presented affective face or word matched the affective stimuli presented *n* positions back. Another important advantage of the neurofeedback paradigm proposed for treating depressed patients is the presence of feedback which can guide their dysfunctional emotion regulation system.

Various studies have investigated the application of imaging-based neurofeedback in other clinical syndromes such as chronic pain (DeCharms et al., 2005), Parkinson's disease (Subramanian et al., 2011), tinnitus (Haller,

Birbaumer, & Veit, 2010), stroke (Sitaram et al., 2012) and schizophrenia (Ruiz et al., 2013). Although increasingly more pilot studies of clinical applications of imaging-based neurofeedback have been published in recent years, this technique is clearly still in its infancy and its full potential still has to be uncovered. Future studies might demonstrate the feasibility of applying this method to for instance addiction and autism as well and are likely to provide more insight in its value in clinical settings.

Apart from a potential role in the treatment of various disorders, the advantages that neurofeedback training provides as a research tool must not be forgotten. The (parametric) modulation of brain activation that can be achieved via neurofeedback can provide useful insights in brain-behaviour relations. Related to this, the study described in Chapter 4 investigated the effect of activity changes in higher order visual areas on perception. Although no perceptual changes were found, these may have been present but not picked up by the selected measures of perception. This study did however confirm the findings of Weiskopf et al. (2004) and incorporated two important improvements. First of all, it was shown that healthy participants can learn to differentially activate higher visual areas, mediated not by eye movement but by imagery techniques. Conversely, Weiskopf et al. had selected two brain areas with relatively unrelated functions. While the SMA has a more direct bearing to motor functions, the PPA is more involved in scene encoding. Our study employed two areas that were both involved in higher order visual processing, thereby increasing the task difficulty. Secondly, in contrast to Weiskopf et al. and many other neurofeedback studies to date, our study excluded a confounding effect of eye movement. Moreover, we collected physiological data to account for any variation in for instance heart rate during the self-regulation and count condition. Despite the known effects of physiology on the blood oxygenation level dependent (BOLD) response (Birn, Murphy, Handwerker, & Bandettini, 2009), neuroimaging-based neurofeedback studies rarely collect these measures. Future studies should show more awareness of potentially confounding variables and take appropriate measures. Any other directions for future studies will be discussed next.

9.3 Future directions

It is of interest to find out which people are more receptive to the neurofeedback procedure than others. This is of especial importance given the potential selection bias in the current sample, as patients signing up for research may differ from a typically depressed patient especially given that patients had to lie in the MRI scanner for a number of hours. It is possible that depressed patients suffering from severe co-morbid anxiety would struggle with the relatively confined and noisy environment of the scanner. Young et al. (2014) found that depressed patients who indicated to have more difficulty with describing feelings were less able to regulate their amygdala activation. It will be interesting to see if other neurofeedback studies targeting emotion processing areas replicate this finding. Another factor that may influence up-regulation performance is an individual's ability to use vivid imagery. Therefore, it would have been useful to administer the VVIQ in the depression study too, especially because the self-regulation task had to be performed with open eyes. Although the VVIQ was filled out by the healthy volunteers in the study described in Chapter 4, the variability in measured scores was too low to investigate any relation between VVIQ score and up-regulation performance.

Previous studies have found that a successful course of cognitive behavioural training (CBT) was concomitant with several changes in brain activation such as the amygdala and caudate nucleus no longer showing an exaggerated response to neutral pictures. Also a normalisation of the negativity bias in the left anterior temporal lobe and VLPFC have been found (Ritchey et al., 2011). Given some of the similarities between CBT and neurofeedback, it will be of interest to see if patients who experienced a clinical improvement in the current study showed corresponding alterations in brain activation during the emotion localiser after five neurofeedback sessions.

Another facet of interest is the transferability of self-regulation skills acquired in the scanner and, related to this, the economical costs involved with neurofeedback treatment for depression. Patients filled out the European quality

of life (EQ-5D) scale and a resource use questionnaire to investigate the socioeconomic benefit of neurofeedback training (findings not reported in present thesis). Although at first sight the costs of neurofeedback may seem disproportional given the involvement of the relatively costly MRI scanner, the estimated cost of a five-session course of neurofeedback treatment is estimated to be just over £500 more expensive than half a year of weekly CBT. If CBT is charged at £60 per session, the overall costs would amount to £1560. If one neurofeedback session involves £375 in scanning costs and £60 in staff costs, the overall costs for five sessions would amount to £2175. Although neurofeedback treatment may be more expensive than CBT in the short-term, the clinical improvements caused by neurofeedback training may occur over a shorter time span thereby reducing socioeconomic costs. The costs associated with any booster sessions that may be required to sustain self-regulation ability may outweigh the costs involved with for instance occupational role impairment. In addition, optimisation of the self-regulation practise that patients conducted at home, may promote the transfer of self-regulation ability to settings where no feedback is provided. Some patients may for instance benefit from incorporating pictures of their positive memories in the homework CD, which can serve as a reminder of successful strategies and may help in transferring and sustaining self-regulation ability.

As described in Chapter 8, future steps to improve neurofeedback training include the testing of neurofeedback paradigms incorporating multi-voxel activation patterns but also the connectivity strength between areas relevant to the behaviour of interest. Koush et al. (2013) were the first to provide healthy participants with near real-time feedback derived from dynamic causal modelling. Participants were then asked to modify the effective connectivity between either the visual and parietal cortex in the right hemisphere, or in the left hemisphere. This task was successfully executed by covertly shifting visuo-spatial attention to either the right or left visual field. The disadvantage of feedback from connectivity measures compared to pattern classifiers is the requirement of *a priori* knowledge of the areas involved in the task of interest. Sitaram et al. (2011) pioneered in training healthy volunteers with feedback from a real-time support vector machine (SVM) classifier decoding affective

states of happiness and disgust. The classifier was incrementally retrained after each feedback session to account for brain activation changes concomitant with performance improvements. Nevertheless, the classifier performance during the provision of feedback was significantly less accurate compared to sessions without feedback. This is not surprising given the activation patterns that feedback can induce which will not have been present in the training dataset. However, this poses an important challenge if the brain-state patterns of healthy individuals during emotional processing were to be used to train patients with dysfunctional affect. The non-simultaneous presentation of self-regulation trials and feedback might be able to circumvent this problem.

Apart from the potential use of, perhaps refined, neurofeedback paradigms as an add-on treatment tool, it might also promote the effectiveness of other treatment methods. For instance, neurofeedback training could be used to assess a suitable location for deep brain stimulation (DBS) in depression or obsessive-compulsive disorder, by ensuring the functional involvement of the area to be stimulated by DBS. Although DBS of the subgenual anterior cingulate cortex (sgACC) is most common in depression, several other target areas such as the nucleus accumbens (Schlaepfer et al., 2008) and ventral capsule/ventral striatum (Malone Jr et al., 2009) have been investigated as well. Given the various types of depression, some targets might be more suitable for some patients than others. Neurofeedback training could confirm the involvement of a putative target area for DBS in for instance emotion processing and result in an initial change in activation. Subsequent changes in activation could then be facilitated by DBS to this site.

In conclusion, the findings presented in this thesis suggest that real-time fMRI-based neurofeedback training is a suitable method to target not only the cognitive but also the biological substrate of depression. At the same time, it offers a non-invasive, individually tailored way of treatment without any side-effects. There is also ground to believe that neurofeedback training might be effective before a full-blown episode of depression is experienced and before maladaptive response styles have firmly rooted. The vicious cycle of developing negative schemata that result in negative cognitive biases, which in

turn affect behavioural and environmental responses could thereby potentially be prevented. The exact contribution of real-time fMRI-based neurofeedback to alleviate symptoms of depression remains to be seen and the results of the ongoing clinical trial will play an important role in scrutinising this.

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Appendix – Additional table Chapter 8

Regions underlying different valence conditions reported per contrast

	Region	**TAL**	**NrOfVoxels**
Contrast positive - negative			
Positive weight			
	IFG	51, 7, 15	27
		-39, 37, -3	27
	Medial frontal gyrus	18, 42, 24	27
	OFC	33, 43, 10	45
	STS	-45, -23, -15	81
	OTG	33, -41, -18	108
	Parahippocampal gyrus	-24, -25, -18	180
	Postcentral gyrus	-36, -30, 29	333
		18, -31, 40	117
	IPL	57, -27, 25	378
		-36, -35, 32	204
	Supramarginal gyrus	45, -46, 36	108
	Retrosplenial area	12, -39, 0	216
	Insula	39, 11, -1	189
		-33, -13, 3	459
	Putamen	30, 4, -1	81
	Caudate nucleus	18, -5, 18	54
	Hippocampus	27, -32, 0	27
		-6, 56, 9	54
	Hypothalamus	9, -9, 3	27
		-9, -7, -6	108
Negative weight			
	IFG	48, 7, 23	447
		-48, 20, 19	309
	MFG	-33, 4, 28	570
		48, 31, 27	135
	SFG	18, -22, 51	480
	Medial frontal gyrus	12, 43, 31	396
	MTG	57, -45, 2	381
		-57, -18, -9	27
	STS	42, -27, -1	441
		-39, -25, -9	90
	STG	-30, -33, 4	423
	OTG	-39, -41, -15	27

	Parahippocampal gyrus	38, -29, -7	270
	Precentral gyrus	-48, -19, 40	279
	IPL	60, -34, 24	27
	Supramarginal gyrus	36, -38, 32	159
	Heschl's gyrus	-33, -36, 8	256
	Lateral sulcus	60, -39, 21	135
	Planum polare	-45, 7, -16	108
	Gyrus rectus	21, 22, -4	81
	Amygdala	27, -6, -18	123
		-30, -5, -16	81
	Insula	33, -9, 4	180
		-39, -21, 19	198
	Putamen	18, -6, 8	384
		-24, 5, 10	729
	Ventral striatum	18, -12, 7	513
		-18, -6, 11	132
	Hippocampus	-30, -19, -9	27
	Posterior hippocampus	-27, -30, -1	408
	Thalamus	15, -12, 7	495
	ACC	-12, 40, 22	54
	Cingulate gyrus	0, -25, 41	318
		-15, -8, 34	279
	Posterior cingulate gyrus	15, -49, 19	270
		-9, -46, 9	54
	Midbrain	-12, -23, -9	288
	Bilateral diencephalon	0, -5, -6	189
	Cerebellum	0, -33, -15	639

Only activations with a cluster size larger than 10 voxels are listed. TAL = Talairach coordinates of peak activation, NrOfVoxels = Number of voxels, IFG = inferior frontal gyrus, MFG = middle frontal gyrus, SFG = superior frontal gyrus, OFC = orbitofrontal cortex, MTG = middle temporal gyrus, STG = superior temporal gyrus, STS = superior temporal sulcus, OTG = occipitotemporal gyrus, IPL = inferior parietal lobule, ACC = anterior cingulate cortex

	Region	TAL	NrOfVoxels
Contrast positive - neutral			
Positive weight			
	IFG	41, 32, 7	14
	MFG	31, 16, 32	225
	OFC	-30, 40, 7	205
	Supramarginal gyrus	56, -35, 36	3
	STS	54, -2, -15	150
	STG	51, -32, 9	81
		-44, -42, 6	140
	Parahippocampal gyrus	21, -27, -15	289
	Precentral gyrus	-31, -11, 35	441
		-19, -15, -12	88
	Amygdala	24, -5, -19	84
	Insula	43, -14, 16	113
		-30, 19, 11	20
	Putamen	21, -2, 9	95
	Hippocampus	19, -11, -16	18
	Hypothalamus	-12, -16, 3	105
	Cingulate gyrus	12, -38, 45	19
		-8, -9, 35	302
Neutral weight			
	IFG	36, 50, 14	274
		-44, 24, 9	87
	SFG	23, 31, 33	382
	Medial frontal gyrus	-9, 49, 36	366
	OFC	23, 52, 4	112
	ITG	-47, -27, -16	123
	STG	-42, 2, -18	271
	STS	51, -16, -7	195
		-28, -33, 2	355
	OTG	38, -2, -22	529
		-33, -26, -18	18
	Precentral gyrus	24, -28, 43	829
		-37, -22, 35	283
	Postcentral gyrus	-33, -38, 45	49
	IPL	47, -29, 28	174
		-37, -33, 32	350
	Supramarginal gyrus	-42, -38, 33	350
	Precuneus	15, -51, 41	502
		-1, -46, 37	267

	Retrosplenial area	-12, -48, 1	269
	Insula / IFG	48, 7, 9	274
	Insula	38, 5, 21	616
		-31, -31, 24	416
	Caudate nucleus	21, -5, 22	498
		-10, 14, -4	540
	Putamen	29, -14, 11	553
		-16, 3, 5	
	Posterior hippocampus	26, -26, 5	403
	Thalamus	-12, -10, 12	303
	Subgenual cingulate	9, 28, -5	502
	Subcallosal gyrus	13, 17, -10	627
	Cingulate gyrus	1, 3, 28	164
	Posterior cingulate gyrus	-13, -36, 30	937
	Cerebellum	-30, -38, -29	127

Only activations with a cluster size larger than 10 voxels are listed. TAL = Talairach coordinates of peak activation, NrOfVoxels = Number of voxels, IFG = inferior frontal gyrus, MFG = middle frontal gyrus, SFG = superior frontal gyrus, OFC = orbitofrontal cortex, ITG = inferior temporal gyrus, MTG = middle temporal gyrus, STG = superior temporal gyrus, STS = superior temporal sulcus, OTG = occipitotemporal gyrus, IPL = inferior parietal lobule

	Region	TAL	NrOfVoxels
Contrast neutral - negative			
Neutral weight			
	IFG	50, 26, 6	33
		-45, 24, 7	121
	MFG	-25, -2, 42	50
	Medial frontal gyrus	-8, 37, 41	26
	ITG	-42, -41, -23	127
	MTG	59, -41, -3	149
	STS	53, -23, -3	198
	OTG	35, -20, -24	16
	Precentral gyrus	24, -29, 43	33
		-31, -6, 32	231
	Postcentral gyrus	35, -33, 32	21
	IPL	-61, -36, 16	58
	Insula	33, -12, 24	70
	Caudate nucleus	24, -14, 24	344
	Putamen	-23, -8, 10	467
	Ventral striatum	25, -22, 12	538
	Hippocampus	23, -12, -4	438
		-21, -11, -7	38
	Thalamus	14, -10, -9	271
	Subcallosal gyrus	-4, 10, -12	32
	Subgenual cingulate	-10, 22, -3	75
	ACG	13, 35, 31	367
	Cingulate gyrus	-12, -7, 36	64
	Posterior cingulate	-7, -34, 24	213
	Midbrain	14, -14, -9	273
		-13, -10, -2	304
Negative weight			
	IFG	50, 0, 10	124
	SFG	-23, 36, 27	36
	OFC	35, 37, 10	243
	ITG	54, -47, -14	84
	OTG	31, -33, -16	419
		-25, -27, -21	13
	Parahippocampal gyrus	-28, -41, -11	57
	Precentral gyrus	-43, -15, 40	20
		33, -22, 39	35
	TPJ	48, -36, 13	215
	Amygdala	29, -4, -15	160
	Insula	38, -10, 8	450
		-26, 21, 9	188

	Thalamus	-19, -24, 2	16
	Cingulate gyrus	16, -15, 33	222
	Midbrain	-15, -23, -7	178

Only activations with a cluster size larger than 10 voxels are listed. TAL = Talairach coordinates of peak activation, NrOfVoxels = Number of voxels, IFG = inferior frontal gyrus, MFG = middle frontal gyrus, SFG = superior frontal gyrus, OFC = orbitofrontal cortex, ITG = inferior temporal gyrus, MTG = middle temporal gyrus, STS = superior temporal sulcus, OTG = occipitotemporal gyrus, IPL = inferior parietal lobule, ACG = anterior cingulate gyrus