The role of dorsolateral prefrontal cortex dysfunction in depression and its treatment with noninvasive brain stimulation

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Declaration

I, Camilla Nord, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Major depression is a common and debilitating condition. However, initial treatment is ineffective for almost half of all patients. This thesis aims to clarify the mechanisms of a novel putative treatment for depression, transcranial direct current stimulation (tDCS), which targets the dorsolateral prefrontal cortex (DLPFC). The first experimental chapter tests whether DLPFC tDCS alters emotional face perception, akin to the acute effects of antidepressant drugs. Our analyses revealed that tDCS does not exert an antidepressant-like effect on emotion perception, but may affect non-emotional cognition. The second experimental chapter examines neural activation in depressed patients, unaffected first-degree relatives of depressed patients, and healthy controls during the n-back working memory task and a facial emotion processing task. During the n-back, depressed patients showed pronounced DLPFC hypoactivation, while at-risk participants were indistinguishable from healthy controls, consistent with the hypothesis that DLPFC dysfunction might be a useful target for depression treatment. In the final two chapters, I report results from a double-blind randomized controlled trial that for the first time tested DLPFC tDCS as an augmentation strategy to psychotherapy in depression, measuring its neural, cognitive, and clinical effects. On the primary outcome measure (observer-rated depressive symptoms) active tDCS did not show a significant improvement over sham stimulation, although the difference was in the hypothesised direction. However, baseline DLPFC activation during the n-back strongly predicted clinical outcome, with this association specific to the active tDCS condition. Thus, baseline DLPFC activation might serve as a putative ‘biomarker’ for clinical response to tDCS. In the general discussion, these experimental findings are discussed in the context of contemporary theories of depression. This thesis adds new insights into the possible mechanisms of tDCS as a treatment for depression. It also demonstrates the added value of neuroimaging to psychiatry clinical trials, highlighting a potential role for predicting treatment outcome.

Acknowledgments

Most of all, I would like to thank my supervisor, Jonathan Roiser. Jon has been an extraordinary teacher to me, a source of insight, and a mentor. Working with him has been the best part of my PhD, and I cannot say with certainty that I would have become a scientist if I had not met him.

In Queen Square, I have been extremely fortunate to work with so many brilliant scientists and people. I would like to thank Sven Bestmann, for co-supervising my PhD and showing me the forefront of tDCS research; my former supervisor, Joel Winston, for being a particular scientific inspiration; and my colleagues and friends in the Roiser lab: Niall Lally, Caroline Charpentier, Anahit Mkrchian, Maddy Payne, and Rick Adams, who have been a joy to work with and helped me on so many occasions, Chamith Halahakoon, whose conversations made my office life significantly more fun, Vincent Valton, for being a constant source of support and co-writing one of the papers I am proudest to have published; as well as Oliver Robinson and Jessica Aylward for their invaluable help during my PhD. I would also like to thank the Institute of Neurology and Brain Research Trust for their generous financial support over the past four years. Lastly, I am grateful to my favourite collaborator, whom I met in Queen Square six years ago, Becky Lawson.

For making the trial possible, I would in particular like to thank Steve Pilling, Judy Leibowitz, Tarun Limbachya, and the team of therapists who agreed to take on trial patients: Karen Katz, Robin Weedon, Michaela Thomas, Jeremy Handel, Flavia Cigolla, Chinea Eziefula, Akbar Jamil, Isabella Foustanos, Abi Harris, Alex Turner, and Sukhvinder Virdee. I would also like to thank Phil Cowen, Eileen Joyce, and John Rothwell, for sitting on the trial steering committee and advising me on a number of issues throughout the duration of the trial. Of course, there would also be no trial had I not found 39 patients generous enough with their time to volunteer to take part (I am also grateful to the 135 healthy participants for taking part in my other experiments, but you were admittedly easier to find).

Finally, I am grateful to my family, Roger, Deborah, and Nicholas, for a lot more than the four years of this PhD, but I haven't written acknowledgements for the other twenty-three years so I suppose this will have to do.

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List of abbreviations

ACC	Anterior cingulate cortex
ANOVA	Analysis of variance
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BOLD	Blood oxygen level-dependent
CBT	Cognitive behavioural therapy
CCT	Computerized cognitive therapy
DBS	Deep brain stimulation
DLPFC	Dorsolateral prefrontal cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECT	Electroconvulsive therapy
EEG	Electroencephalography
EPI	Echo-planar imaging/image
fMRI	Functional magnetic resonance imaging
FSIQ	Full-scale intelligence quotient
FWE	Family-wise error
HAM-D	Hamilton Rating Scale for Depression
IAPT	Improving Access to Psychological Therapies service
ICC	Intraclass correlation coefficient
IPT	Interpersonal therapy
ITT	Intention-to-treat
mA	Milliamps
MATLAB	Matrix laboratory
MDD	Major depressive disorder
MINI	Mini International Neuropsychiatric Interview
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging

NHS	National Health Service
OCD	Obsessive compulsive disorder
OFC	Oribitofrontal cortex
PD	Parkinson’s disease
PET	Positron emission tomography
PFC	Prefrontal cortex
PPC	Posterior parietal cortex
PTSD	Post-traumatic stress disorder
RCT	Randomized controlled trial
ROI	Region of interest
SD	Standard deviation
sgACC	Subgenual anterior cingulate cortex
SHAPS	Snaith-Hamilton Pleasure Scale
SPECT	Single-photon emission computed tomography
SPM	Statistical parametric mapping
SPSS	Statistical Package for the Social Sciences
SSRI	Selective serotonin reuptake inhibitor
SVC	Small volume correction
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
VIF	Variance inflation factor
WTAR	Weschler Test of Adult Reading

List of Figures and Tables

Notes to examiners

The findings from Chapter 3 have been published in a peer-reviewed article:

Nord CL, Forster S, Halahakoon DC, Penton-Voak IS, Munafò MR, Roiser JP (2017). Prefrontal stimulation does not affect emotional bias, but may slow emotion identification. *Social Cognitive and Affective Neuroscience* 12(5): 839-847.

Portions of Chapters 1 and 6 have been published in two peer-reviewed articles:

Nord CL, Roiser JP Non-invasive direct current brain stimulation: the evidence behind the hype (2015). *Advances in Clinical Neuroscience and Rehabilitation* 15(5): 9-11.

Nord CL, Gray A, Charpentier CJ, Robinson OJ, Roiser, JP (2017) Unreliability of putative fMRI biomarkers during emotional face processing. *NeuroImage* 156: 119-127.

The work reported in this thesis is entirely my own except for the contributions acknowledged below. My supervisor, Prof. Jonathan Roiser, has contributed comments and guidance on all chapters of the thesis.

In Chapter 3, data from a subset (~15% of the total sample) was collected by a clinical research associate in Prof. Roiser's group, Dr. Chamith Halahakoon. This study also benefited from collaborations with Dr. Sophie Forster (University of Sussex), and Professors Marcus Munafo/Ian Penton-Voak (University of Bristol), who provided code for the distractibility and emotion identification tasks, respectively.

In Chapter 5, delivery of a minority of the stimulation sessions (<20%) was conducted by either Dr. Halahakoon or a low-intensity therapist in the NHS Psychological Treatment Service, Tarun Limbachya (who also assisted with patient recruitment); two sessions each were conducted by Jessica Aylward and Alan Gray, research assistants at in Prof. Roiser's group.

Chapter 1: General Introduction

1.1 Major depressive disorder

Written descriptions of depression date as far back as classical antiquity. In his *Aphorisms*, Hippocrates defines a melancholy as a “fright or despondency which lasts for a long time,” characterised by an “aversion to food, despondency, sleeplessness, irritability, and restlessness” (Hippocrates). In perhaps the earliest medical theory of depression, he attributes melancholic states to cerebral dysfunction resulting from an excess of black bile, one of the four humours according to the Ancient Greeks. Ishaq ibn Imran, a physician in Baghdad circa 900 A.D., suggested that “melancholy is a feeling of dejection and isolation which forms in the soul because of something which the sufferer thinks is real but which is actually unreal” (Davison, 2006). These early descriptions illustrate the nature of depression as linked to typical feelings (despondency; dejection; isolation) but transcending the normal bounds of emotions, lasting longer and incurring substantial physiological and psychological disturbance.

The current Diagnostic and Statistical Manual of Mental Disorders (DSM-5) requires at least two weeks of a substantially lowered mood and/or a loss of interest of pleasure in daily activities to meet criteria for major depressive disorder (also known as unipolar depression) (American Psychiatric Association, 2003); these symptoms, also known as dysphoria and anhedonia, are the cardinal symptoms of depression. In addition, four (or three if both cardinal symptoms are present) of the following symptoms are required to have been present nearly every day: significant weight change or change in appetite; activity changes (psychomotor agitation or

retardation); fatigue or loss of energy; guilt or worthlessness; concentration difficulties; suicidality; and insomnia or hypersomnia (one of Hippocrates' *Aphorisms* also states: "both sleep and insomnolency, when immoderate, are bad").

The ICD-10 uses broadly similar, though not identical criteria: in addition to low mood and anhedonia, fatigue (or low energy) is considered a key symptom (World Health Organization, 1992). Patients experiencing any of these three key symptoms (most of the time for at least two weeks) are then asked about the remaining six symptoms in the DSM diagnostic criteria, with the addition of a seventh symptom, low self-confidence. From this, the degree of depression is designated as 'not depressed' (presenting with fewer than four symptoms); 'mild depression' (four symptoms); 'moderate depression' (five or six symptoms); or 'severe depression (seven or more symptoms, with or without psychotic symptoms).

It is notable that to meet DSM diagnostic criteria for depression, the above symptoms must not only be present but must produce a functional impairment. This is common to all psychiatric disorders, and originates from the psychiatrist Robert Spitzer. Tasked with deciding whether or not to include homosexuality as a diagnosis in the DSM-II, Spitzer feared that eliminating homosexuality from the DSM-II would give weight to antipsychiatrists' claims that *all* diagnoses were merely artificial social constructs (Lieberman and Ogas, 2015). To resolve this, he invented the concept of *subjective distress*, requiring any psychiatric diagnosis to cause emotional distress or functional impairment, which would prove fundamental to future editions of the DSM. In the current DSM, the diagnostic criteria for a major depressive episode require symptoms to have caused clinically significant distress or impairment in social, occupation, or other important areas of functioning (American Psychiatric

Association, 2003). Arguably, this functional impairment is also one of the most important measures of a successful intervention.

Today, depression is the leading global cause of disability, affecting more than 300 million people worldwide (World Health Organization, 2017). It contributes to significant premature mortality, due to elevated suicide rates and circulatory disorders in depressed patients (Angst et al., 2002). Together, depression and anxiety cost the global economy $1 trillion each year, equivalent to nearly 1/3 of the UK's gross domestic product (GDP) (Chisholm et al., 2016). Despite extensive research for new treatment targets, pharmacological and psychological interventions for depression have changed little in the past thirty years. The difficulty in developing new treatments arises in part because depression is a syndrome of unknown and possibly heterogeneous aetiology. However, both pharmacological and psychological treatments alter a number of neural and cognitive abnormalities in depression, shedding light on the origins of the disorder, and potentially informing the development of novel interventions.

In the first half of this introductory chapter, I will describe how two of the most common treatments for depression, antidepressant medication and psychotherapy (in particular cognitive behavioural therapy: CBT) might alter the major neural circuitry disrupted in depression. I will synthesize research showing evidence for the effect of antidepressant medication on low-level affective biases, the effect of CBT on high-level negative schemata, and the role of non-emotional cognition (in particular cognitive control) on the effectiveness of both treatment types. I will describe how these findings are integrated in the cognitive neuropsychological model of depression (Harmer et al., 2009a; Roiser et al., 2012). From this basis, I will

hypothesize how the cognitive neuropsychological model might account for the antidepressant effects of experimental non-invasive neurostimulation treatments in depression, in particular transcranial direct current stimulation (tDCS).

In the second half of the chapter, I will review the neurophysiological, behavioural and neural circuit effects of tDCS, before evaluating the efficacy of dorsolateral prefrontal cortex (DLPFC) tDCS as a treatment for depression. Next, I will explain the logic underlying a prediction that DLPFC tDCS exerts its beneficial effects in depression through its actions on top-down cognitive control, via direct modulation of the DLPFC. This is consistent with one of the hypotheses of the cognitive neuropsychological model, that cognitive control (and corresponding DLPFC activity) might both confer resilience against depression and facilitate response to CBT. I will then explain how symptoms of depression might be targeted by combining tDCS of the DLPFC with CBT. Finally, I will outline how I propose to test these hypotheses in this thesis.

1.2 Common treatments for depression

In the majority of patients, depression is treatable. Psychotherapy and antidepressant medication constitute the primary treatment options for the vast majority of patients with depression today. For individuals who fail to respond to either, electroconvulsive therapy (ECT) can also be highly effective, though it is only used in patients who have not benefited from a series of treatments (UK ECT Review Group, 2003). CBT and antidepressant medication have similar efficacies in treating depression (Arroll et al., 2005; Cuijpers et al., 2008a). Traditionally, however, these treatments have been explained via radically distinct mechanisms.

The explanation for effects of antidepressant medication (predominantly selective serotonin reuptake inhibitors, SSRIs, but also drugs that act on the noradrenaline system) is usually couched in terms of neurochemical models of depression (reviewed in more detail in section 1.2.1 below), specifically an increase in monoamine neurotransmission. The classic monoamine hypothesis of depression proposed that such treatments correct an underlying deficiency in monoamine transmission (Coppen, 1967; Cowen and Browning, 2015). While some neuroimaging (Meyer et al., 2006), candidate gene association (Caspi et al., 2003; Kendler et al., 2001), and peripheral biochemical (Banki, 1978; Paul-Savoie et al., 2011) studies support the hypothesis that serotonin is disrupted in depression, findings are generally inconsistent, and the precise nature, direction and role of this disruption remains unclear (Delgado, 2000; Delgado et al., 1999).

In contrast, the explanation for the effects of CBT is usually couched in terms of Beck's classic cognitive model of depression (reviewed in more detail in section 1.2.2 below), in which symptoms originate from stressor-activated latent negative schemata, which directly influence mood and additionally alter basic information processing (Beck, 1979; Disner et al., 2011). In the context of this model, addressing these schemata directly, through CBT, targets the primary psychological mechanism that gives rise to symptoms.

1.2.1 Antidepressant medication

The discovery of antidepressant drugs began when patients with tuberculosis were treated with iproniazid and reported mood-elevating side effects. Within a year of publishing a report on these effects, over 40,000 depressed patients were treated with iproniazid (Shulman et al., 2013). Soon thereafter, the mechanism of action was

discovered: iproniazid was found to inhibit the enzyme monoamine oxidase. Tricylic antidepressants, which were discovered soon after and elicited less severe side effects than iproniazid, were found to have the same mechanism of action (Shulman et al., 2013).

The discovery of antidepressant medications (and their actions on the monoamine system) caused a paradigm shift in the field of psychiatry, opening a window into investigating the possible neural mechanisms of depression. The finding that antidepressant medications improve mood through monoaminergic-dependent effects contributed perhaps the most influential theory of depression aetiology to date: the monoamine-deficiency hypothesis (Coppen, 1967). The monoamine deficiency hypothesis implicates serotonergic, noradrenergic, and dopaminergic neural circuitry in the aetiology of depression, postulating that depression originates from a deficiency in monoamine transmission in the brain. The monoamine-deficiency hypothesis of depression has had particularly strong predictive power in relation to treatments. Over the decades since the discovery that iproniazid elevated mood, numerous novel compounds typically targeting serotonergic and noradrenergic systems have been developed into effective antidepressant medications (Belmaker and Agam, 2008). These medications have had a prodigious impact on the lives of many depressed patients. The majority of depressed patients eventually respond to a course of antidepressant medication (Arroll et al., 2005); approximately one-third remit after their first course of medication (Rush et al., 2006). Moreover, long term medication treatment (most commonly with antidepressants, but also including medications such as neuroleptics and lithium) substantially lowers suicide rate in depressed patients (Angst et al., 2002).

Proving the central tenet of the monoamine hypothesis – that some deficiency in monoamine neurotransmission exists in patients with depression – has been more difficult. Attempts to evaluate monoamine systems via the plasma, urine, or cerebrospinal metabolites of depressed patients, as well as the brains of post-mortem depressed patients, have yielded largely inconsistent results (Belmaker and Agam, 2008; Ordway et al., 2002). Molecular imaging studies have produced somewhat clearer findings: a meta-analysis of positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies found reductions in midbrain and amygdala serotonin transporter density; this meta-analysis also found a relationship between depression severity and reduction in serotonin transporter density in the amygdala (Gryglewski et al., 2014). However, these reductions were so subtle that no individual study had sufficient power to detect them (Gryglewski et al., 2014). Additionally, the precise interpretation of these results is unclear, as reduced serotonin transporter density should in theory result in an *increase* in serotonin transmission (analogous to the actions of antidepressant drugs). One possibility is that such reductions may reflect a reduced number of serotonin neuron terminals, but direct evidence for this is lacking.

Perhaps the strongest evidence for the involvement of the serotonin system emerges from amino acid depletion studies: dietary depletion of tryptophan, the essential amino acid precursor to serotonin, can induce a transient return of some symptoms in remitted depressed patients (Neumeister et al., 2004). A meta-analysis of monoamine depletion studies found tryptophan depletion decreased mood in remitted patients and healthy controls with a family history of MDD, but not healthy controls (Ruhé et al., 2007). Other studies have inhibited the rate-limiting enzyme in the synthesis of noradrenaline using alpha-methyl-para-tyrosine (AMPT), but this

often has no effect on mood (Ruhé et al., 2007), even in currently-depressed patients (Miller et al., 1996). Thus, reductions in monoamine transmission do not seem to fully account for the complexities of human depression.

Studies over the past few decades have suggested that a course of antidepressant medication seems to normalize the typical dysfunctional pattern of brain activity in depression: hypometabolism in neocortical regions, including prefrontal and parietal cortices, and hypermetabolism in limbic and paralimbic areas (Delaveau et al., 2011; Fitzgerald et al., 2008). A meta-analysis of fMRI studies showed that antidepressant drug treatment increases hypoactive regions in the dorsolateral, dorsomedial, and ventrolateral prefrontal cortices, and decreases hyperactivity of the amygdala, hippocampus, parahippocampal region, ventral anterior cingulate cortex, orbitofrontal cortex, and insula (Delaveau et al., 2011). Activation in some of these regions also seems predictive of clinical response: baseline activation in regions including the subgenual anterior cingulate cortex and the amygdala is associated with response to antidepressant medication (Chen et al., 2007; Davidson et al., 2003; Keedwell et al., 2009, 2010; Langenecker et al., 2007; Siegle et al., 2007a), shedding light on the possible neural mechanisms driving treatment response.

In sum, research on the monoamine hypothesis has shown relatively definitively that the effects of the most common antidepressant drugs on mood are related, at least in part, to their actions on serotonergic and noradrenergic neurotransmitter systems. However, it has not shown definitively that a monoamine deficiency exists in depression (and, if it exists, what aspect of neurotransmission is affected). Indeed, one of the strongest arguments against the monoamine-deficiency hypothesis is that the drugs purportedly remedying this deficiency – antidepressants – have no clinical

effect in up to 40% of patients with depression (Arroll et al., 2005). A meta-analysis of antidepressant efficacy found that in cases of severe depression, antidepressant medication does slightly exceed placebo treatment (i.e., has a small but significant effect size), but seems to have a weaker effect relative to placebo in mild-to-moderate depression (Fournier et al., 2010). Thus, there is a critical need for other effective antidepressant treatments, and with it, a more complete understanding of the neural mechanisms contributing to symptoms.

1.2.2 Psychotherapy

Psychotherapy is the other major class of treatments for depression. It aims to treat mental illness through talking therapy, sometimes in addition to pharmacological therapy. Despite its popularity since the start of the 20th century, until 1970 no study had shown psychological therapy to be more effective than no-treatment control conditions in depression (Kendall and Hollon, 2013). However, the growing rejection of psychoanalytic techniques by the mid-to-late 20th century led many psychiatrists and psychologists to develop new, empirically-tested talking therapies, some of which show treatment efficacies at least equal to antidepressant medication.

There are a number of approaches to psychotherapy, which in general all involve semi-guided dialogue with a therapist. In traditional psychodynamic forms, which derive from psychoanalytical theory, the eventual goal is a patient acquiring insight into the phenomenology and supposed origins of his or her symptoms. In the context of depression, this might involve a patient's exploring early-life experiences or current relationship dynamics that have led to their current feelings of guilt or sadness. Such psychoanalytic forms of psychotherapy do not involve direct manipulation of observable (often behavioural) outcomes (Kendall and Hollon, 2013).

On the other side of the therapeutic spectrum lie behavioural therapies, which aim to explicitly change a patient's maladaptive behaviours. In the context of depression, this might involve setting pragmatic, feasible goals ('see friends', 'apply for job'), but involve little or no discussion of his or her symptoms' origins or phenomenology.

CBT is based on Beck's cognitive theory of depression, in which depression is conceptualised as a disorder of cognitive processing, with emotional biases arising in memory, attention, and interpretation of events. In Beck's model, negative mood is thought to originate from negative thoughts and beliefs; negative thoughts are also thought to impair normal behaviour (Kendall and Hollon, 2013). CBT adopts many of the techniques of purely behavioural therapies (e.g., setting pragmatic goals), but differs from behavioural therapy on several accounts, most notably the use of cognitive techniques (e.g., testing various belief systems) often to attain the same eventual (behavioural) goal as behavioural therapy (Kendall and Hollon, 2013). As a consequence, CBT directly targets negative cognitions in depression, identifying, evaluating, and trying to change maladaptive belief systems and dysfunctional negative information processing (Beck, 1979; Kendall and Hollon, 2013).

Today, CBT is one of the most common and effective treatments for major depression (Churchill et al., 2002) with a similar effect size to antidepressant medication (DeRubeis et al., 2005). Likewise, only about 60% of patients show an adequate response to CBT (Rush et al., 2006). There is some evidence that combined pharmacotherapy and psychotherapy is more effective than antidepressant medication alone, and that the effects of pharmacotherapy and psychotherapy are largely independent from each other (Cuijpers et al., 2014). There also may be a difference in the durability of response: patients treated to remission

with CBT are less likely to subsequently relapse than those treated with antidepressant medication (Gloaguen et al., 1998).

However, a major problem in determining the efficacy of psychotherapy is selection of a control condition. Comparing all psychotherapies to wait-list controls, psychotherapy has a large effect size: Cohen's d=0.88 (Cuijpers et al., 2008b). But comparing to care-as-usual or placebo control groups, this effect size is more than halved (Cohen's d=0.35). This demonstrates the necessity of stringent control conditions in trials evaluating the efficacy of psychotherapies. Unfortunately, there is a relative dearth of psychotherapy trials with adequately strong control arms (such as medication or other bona fide therapies), contributing to highly variable reports of efficacy.

Even using stringent control conditions, the efficacy of psychotherapy interventions for depression varies widely between different therapeutic approaches. A systematic review of 125 clinical trials using psychotherapy to treat major depression found strong evidence to support the use of CBT, interpersonal therapy (IPT), and behavioural therapy in the treatment of depression (Hollon and Ponniah, 2010), while there was only preliminary evidence (i.e, results had not yet been replicated) for the use of brief dynamic therapy and emotion-focused therapy. More traditional psychodynamic, experiential-humanistic, and marital and family approaches were met with little empirical support in clinical trials.

Like antidepressant medication, there is also a substantial proportion of non-responders to psychological therapy (Cuijpers et al., 2008a). Perhaps surprisingly, the finding that antidepressant drugs are efficacious in severe depression but not

milder cases (Fournier et al., 2010) is mirrored for psychological therapies. A meta-analysis of 132 studies found a greater efficacy of psychological therapies in patients with high-severity (Cohen's d=0.63) than in those with low-severity depression (Cohen's d=0.22), when compared with stringent controls (pill placebos or other psychological therapies) (Driessen et al., 2010). This modulatory influence of severity may be driven by a greater efficacy of nonspecific control interventions in remediating milder forms of depression (Hollon and Ponniah, 2010). It may also complicate study design of (and conclusions from) randomised controlled trials (RCTs), if a substantial proportion of patients' depression responds to the expectation of change (whether from a pill or from contact with a therapist).

While some studies show similar neural mechanisms between antidepressant medication and psychotherapy (e.g., normalized prefrontal cortex metabolism (Brody et al., 2001a)), it has been theorized that CBT operates by normalising disrupted prefrontal function in depression (possibly in a manner akin to cognitive training, which is effective in other psychiatric disorders, e.g. (Genevsky et al., 2010)), but that antidepressant medication operates more directly on emotion-dependent regions, such as the amygdala (DeRubeis et al., 2005). Variation in response to CBT can also to some degree be predicted by baseline neural activation. Heightened baseline amygdala activation during emotional processing has been implicated in response to both CBT and antidepressant medication (Siegle et al., 2006, 2007a). By contrast, baseline sgACC deactivation to emotional stimuli seems to differentiate response to medication versus CBT: sgACC deactivation at baseline predicts worse response to antidepressant medication (Chen et al., 2007; Davidson et al., 2003), but better response to CBT (Fu et al., 2008a; Siegle et al., 2006) and behavioural activation therapy (Dichter et al., 2010).

1.2.3 Electroconvulsive therapy

A third common treatment in severe depression is ECT. ECT has been described as the most potent, rapidly-acting antidepressant agent (Perrin et al., 2012), with evidence suggesting it is significantly more effective than drug therapy (UK ECT Review Group, 2003). The effect of ECT on the brain is global and non-specific. While it has been postulated that its antidepressant effects are driven by 'resetting' resting aberrant functional connectivity (Farzan et al., 2014), in fact substantially less is known regarding the neural and cognitive mechanisms of ECT than for antidepressant medication or psychotherapy (Van Waarde et al., 2015). However, it bears mentioning that ECT treatment has also been shown to alter limbic regions (increasing amygdala volume) (Tendolkar et al., 2013) as well as prefrontal regions (decreasing frontal connectivity, centred on the left DLPFC) (Perrin et al., 2012). Sustained reductions in cerebral blood flow following ECT in a network including frontal and temporal cortices were also found to predict clinical response to ECT (Michael et al., 2003). These findings are in keeping with the idea that ECT has wide-reaching effects, potentially an intervention affecting more global cognitive and neural processes than either antidepressant medication or CBT (relatively non-specific treatments themselves).

1.3 The cognitive neuroscience of mood disorders and their treatment

Antidepressant medication and CBT have traditionally been explained within the relatively distinct theoretical frameworks described above (1.2.1 and 1.2.2). More recently, accounts emerging from the cognitive neuroscience literature attempt to explain the effects of both antidepressant drugs and psychological therapies, as well as experimental brain stimulation treatments, within a unitary theoretical framework

based around neural circuit or cognitive findings. In contemporary literature this is usually referred to as the cognitive neuropsychological model (Harmer et al., 2003b, 2009a; Mayberg et al., 1999; Roiser and Sahakian, 2013; Roiser et al., 2012).

These theories arose out of the long literature of cognitive and circuit-level neural abnormalities identified in depression. Depression is marked by a number of changes in perception and information processing, which span both emotional and non-emotional cognition (known as 'hot' and 'cold' cognitive processing, respectively). Non-depressed individuals typically show a bias for positive stimuli, while depressed patients do not; depressed patients are also impaired on many higher cognitive function tasks, such as working memory (Roiser and Sahakian, 2013). These behavioural changes map (approximately) on to two major brain circuits implicated in depression: subcortical limbic activation to emotional stimuli, for example in the amygdala; and prefrontal activation during difficult cognitive tasks, particularly in the dorsolateral prefrontal cortex (DLPFC) (Siegle et al., 2007a).

Prefrontal and amygdala circuits also interact with one another: for example, during top-down control over emotion processing (Ochsner et al., 2004), or in the ability of emotional stimuli to exert bottom-up influence on cognitive tasks (Hare et al., 2005). In an early form of this model it was suggested that depression arises due to dysfunctional prefrontal cortical control over the amygdala, which leads to abnormal emotion processing (Drevets, 1999; Mayberg et al., 1999). Additionally, the subgenual anterior cingulate cortex (sgACC) exerts influence on both dorsal prefrontal regions and the amygdala and insula; numerous studies implicate sgACC disruption in depression, as well as response to treatments for depression (Hamani et al., 2011). As discussed in the next sections, investigating the cognitive

disruptions that occur in depression, and the neural circuitry driving those disruptions, has proven useful in understanding the mechanisms of antidepressant drugs and CBT, and may also provide a framework for conceptualizing novel experimental treatments for depression.

1.3.1 The effect of antidepressant medication on low-level affective biases

In the case of antidepressant medication, the cognitive neuropsychological model of depression has provided useful insight in explaining the delay between the pharmacological action of antidepressant medication (blockade of transporters, which can be detected almost immediately after administration) and their therapeutic effect, which takes several weeks if not months (Frazer and Benmansour, 2002; Harmer et al., 2009a). This model suggests that the time lag in action does not originate purely from a delay in downstream neuroadaptive effects (for example, due to autoreceptor desensitisation (Blier et al., 1987)), but rather that antidepressant medication exerts immediate effects on negative biases in information processing in depressed patients, which over time can improve mood (Harmer et al., 2009a).

This model is supported by extensive empirical studies reporting mood-congruent biases in depression, toward negative and away from positive information processing. This pattern appears in memory, where depressed patients show a bias for remembering negative material (Matt et al., 1992); in perception, as difficulty identifying positive facial expressions (Joormann and Gotlib, 2006); and in attention, where patients are impaired at disengaging from negative emotional stimuli (Mogg et al., 1995). Neuroimaging studies have attributed these affective biases to alterations in limbic circuitry (Leppänen, 2006) and the modulation of these circuits by monoamine neurotransmission (Harmer et al., 2009a; Roiser and Sahakian, 2013).

For example, depressed patients exhibit substantially more intense and prolonged amygdala reactivity to self-relevant negative information than healthy controls (Siegle et al., 2002), and greater amygdala responses to masked emotional faces, both of which normalize with antidepressant treatment (Sheline et al., 2001; Victor et al., 2010). In addition, dysfunction in the sgACC is thought to influence a wide network of self-referent processes attributed to the default-mode network (DMN), a network of brain regions active during the resting state (and attenuated during cognitive processing) (Greicius et al., 2003), including the ventromedial PFC and posterior cingulate cortex (Hamilton et al., 2015). Increased sgACC-DMN functional connectivity predicts levels of depressive rumination, repetitive and self-reflective depressive thoughts (Hamilton et al., 2015), often considered a central aspect of the phenomenology of depression (Lyubomirsky et al., 1999). Rumination could be conceptualised as an affective bias in mind-wandering; mind-wandering itself negatively correlates with happiness (Killingsworth and Gilbert, 2010), and has been suggested as a marker for depressive thinking (Smallwood et al., 2007).

The cognitive neuropsychological model provides a common framework between Beck's cognitive theory of depression (and the effects of CBT) and the mechanisms of antidepressant medication (see Figure 1.1). According to this model, low-level negative biases instantiated by aberrant responses in limbic circuitry contribute to the development of negative schemata (Roiser and Sahakian, 2013). In support of this, such emotion processing biases seem to coincide with vulnerability to depression: they are found in never-depressed people with high neuroticism, a risk factor for depression (Chan et al., 2007), and in unaffected first-degree relatives of depressed patients (Le Masurier et al., 2007).

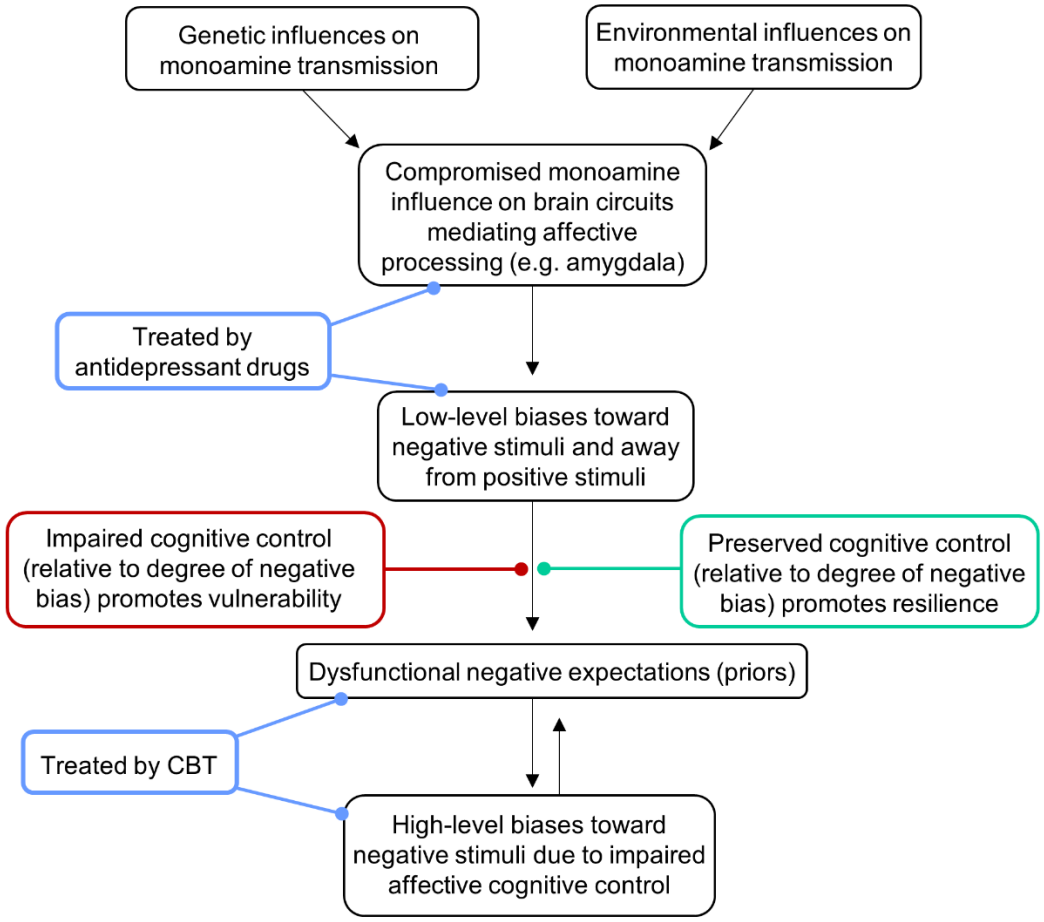

Figure 1.1 The cognitive neuropsychological model of depression. Black boxes contain factors contributing to depressive symptoms; blue boxes indicate which aspects of the model are targeted by treatments; and red and green boxes indicate risk and resilience factors, respectively. Figure adapted from Roiser, et al. (2012), *Neuropsychopharmacology*.

Crucially, both cognitive and neural measures of low-level negative biases can be reversed by antidepressant drugs relatively quickly. A single dose of the noradrenaline reuptake inhibitor reboxetine improves positive facial expression recognition and memory for positive information in depressed patients, despite inducing no change in mood (Harmer et al., 2009b). Even in healthy controls (who do not show any modulation of mood by chronic antidepressant treatment), a single dose of the SSRI citalopram increases positive facial expression recognition (Harmer et al., 2003a) and attentional bias towards positive cues (Browning et al., 2007) (though it should be noted that in this study citalopram also increased processing of

anxiety-related stimuli). Neuroimaging studies have found that a single dose of citalopram acutely reduces amygdala responses to fearful faces in healthy controls (Murphy et al., 2009). Short-term (7-day) treatment with citalopram also normalises amygdala hyperactivation in depressed patients (Godlewska et al., 2012); the same group found these short-term changes in emotional processing were also predictive of long-term clinical outcome (Godlewska et al., 2016).

In summary, empirical work strongly supports the existence of negative biases in depression; the normalisation of these biases with acute doses of antidepressant medication; and the role of the limbic system, particularly the amygdala, in mediating negative biases and their alleviation with antidepressant medication.

1.3.2 The effect of CBT on high-level negative schemata

As described above, in the framework of the cognitive neuropsychological model antidepressant medication directly targets low-level negative biases; for example, shifting negatively biased perceptions of emotional stimuli more positively (see Figure 1.1). The model propoes that in patients who respond to antidepressant medication, repeated exposure to these more positive perceptions – decreasing or eliminating negative perceptual biases – eventually improves mood. However, mood improvement can only take place if a second set of biases are sufficiently malleable: higher-level emotional biases, which can be conceptualised as negative expectations, termed schemata by Beck.

In Beck's cognitive theory, these negative schemata entail an expectation of negative information. Negative schemata may be thought of as a Bayesian prior expectation or belief: a model of the world that heavily influences all information

processing. In the case of depression, a highly precise prior for negative outcomes could outweigh the influence of positive input, such that no amount of positive perceptions can override the negative expectation. In turn, low-level biases could both contribute to and be induced by strong negative expectations. In the cognitive neuropsychological model, negative schemata arise, at least in part, due to the cumulative influence of low-level emotional biases, which can alter prior expectations and thereby contribute to negative schemata.

Antidepressant drugs may show a weaker ability to treat patients with particularly entrenched negative schemata (which can be thought of as very precise Bayesian priors). CBT is thought to address top-down biases more directly than antidepressant drugs, a mechanism that could be underpinned by effects on the prefrontal cortex (DeRubeis et al., 2005). CBT aims to challenge and undermine the perceived accuracy of high-level negative biases (in other words, resolve negative schemata) by training patients to challenge their negative expectations. If these prior expectations are malleable, CBT weakens negative expectations, and could also have indirect effects on low-level negative biases. However, in contrast to antidepressant medication, CBT does not directly ameliorate low-level negative biases. In keeping with this, amygdala activation does not always normalize following treatment with CBT (or IPT) (Brody et al., 2001b; Goldapple et al., 2004; Martin et al., 2001). As such, according to this model, patients with particularly strong low-level negative biases may be resistant to a course of CBT without concurrent medication.

1.3.3 Cold cognitive impairments in depression

According to the cognitive neuropsychological model, whether or not high-level negative expectations can be challenged (either in a clinician-directed manner

through CBT, or independently by patients) is heavily dependent on a feature of depressive illness thought to be separate to the emotion processing findings reviewed so far: cold (or non-emotional) cognitive processing. Cold cognitive deficits contribute to a diagnostic criterion of depression, concentration difficulties, which manifests as indecisiveness and a diminished ability to think or concentrate (American Psychiatric Association, 2003). Cold cognitive impairments also likely contribute to a significant portion of the functional impairment experienced in depression, including deterioration of performance at work or school.

Altering negative expectations – the goal of CBT – is a cognitively effortful process. The process of challenging one's own entrenched negative beliefs involves working memory, reality monitoring, counter-factual thinking and emotional regulation (a form of inhibitory control). As such, successful CBT is thought to rely heavily on one aspect of cold cognition in particular: cognitive control (Roiser and Sahakian, 2013). It has been suggested that deficits in cold cognition might compromise patients' abilities to benefit from psychological therapies (Roiser and Sahakian, 2013) (see Figure 1.1). Particularly if negative expectations are strongly entrenched – if the Bayesian prior for negative outcomes is very precise – deficits in cold cognition could weaken patients' ability to challenge their negative expectations through CBT.

The same may be true for antidepressant medication. According to the model, while antidepressant drugs directly target low-level negative biases, changes in these low-level perceptions can only positively influence negative expectations (and ultimately mood) if patients engage with reality-monitoring. This process allows positive perceptions and outcomes to gradually reshape expectations, but is likewise effortful and may be dependent on intact cognitive control. These predictions are

substantiated by studies finding that executive function deficits predict poor response to antidepressant medication (McLennan and Mathias, 2010), and in older adults, non-response to antidepressant treatment was predicted by attenuated prefrontal responses (Potter et al., 2004).

Cold cognitive deficits in depression may in particular be driven by aberrant processing in the DLPFC. Abnormal metabolism in the DLPFC is one of the most established neural correlates of depression: resting-state studies (e.g. using PET) have largely reported reductions in DLPFC metabolism in depressed patients (Baxter et al., 1989; Biver et al., 1994; Galynker et al., 1998), which normalizes somewhat following symptom remission (Brody et al., 2001a). By contrast, task-related activation (e.g. during working memory) in depression is sometimes increased (Harvey et al., 2005; Wang et al., 2015), but in other cases decreased (Fales et al., 2009). This may be accounted for by between-study differences in task difficulty: a meta-analysis examining only studies where working memory performance was matched between depressed patients and healthy controls found DLPFC hyperactivation in depressed patients (Wang et al., 2015). Lesion studies also support findings of DLPFC dysfunction in depression: patients with lesions incorporating the DLPFC show higher levels of depression than those whose lesions spare the DLPFC (Koenigs and Grafman, 2009). Normalising DLPFC activity is thought to be critical to effective CBT (DeRubeis et al., 2005) and antidepressant treatment (Fales et al., 2009), as originally posited in an early form of the cognitive neuropsychological model (Mayberg et al., 1999).

In theory, boosting cold cognition should improve response to both major forms of treatment for depression (CBT and medication). One meta-analysis found that

cognitive impairments persist even in patients whose depressive symptoms have remitted (Rock et al., 2014). In the case of medication, antidepressant treatment *per se* does not appear to improve cold cognition (Halahakoon and Roiser, 2016; Shilyansky et al., 2016). However, better cold cognition may make patients more likely to engage in reality-monitoring during antidepressant treatment, allowing positively-shifted low-level biases to indirectly change negative expectations. For CBT, improved cold cognition might make patients more able to engage in the types of effortful cognitive processes that CBT requires. There is some evidence that enhancing cold cognition has knock-on effects on mood: cognitive training improves mood in patients with dementia (Davis et al., 2001; Loewenstein et al., 2004; Sitzer et al., 2006) and geriatric patients with depression (Arean et al., 1993; Motter et al., 2016). Pharmacological interventions that enhance cold cognition have also been shown to improve antidepressant therapy. A meta-analysis revealed that the stimulant-like agent modafinil, which improves executive function in depression (DeBattista et al., 2004), significantly augmented the effects of first-line medications for unipolar and bipolar depression (Goss et al., 2013). Similarly, several studies (and one RCT) show that targeting cognitive deficits with erythropoietin has effects on mood, as well as on measures of cold cognition (Miskowiak et al., 2012, 2014) and DLPFC activation (Miskowiak et al., 2016).

1.3.4 Future directions for the cognitive neuroscience of mood disorders

According to the cognitive neuropsychological model, in patients who respond to antidepressant medication, mood improvement will occur after several weeks of experiencing the world with more positive perceptions and immediate interpretations of environmental stimuli. In these patients, the actions of antidepressant drugs on

monoaminergic systems in limbic regions, and resulting effects on negative biases (Harmer et al., 2003b), is sufficient to alleviate depression. In others, these changes in low-level biases will be inadequate because high-level expectations (priors) are very precise and/or cold cognitive impairment is sufficiently severe to maintain them. Using this logic, cognitive and fMRI tests assessing cognitive control could identify patients as likely responders (or nonresponders) to antidepressants.

Therefore, one potential direction emerging from cognitive neuroscience studies of depression is the stratified delivery of existing treatments according to patients' brain activation in specific structures/circuits, or behaviour on relevant cognitive tasks. Potentially, treatment plans could be adjusted according to baseline performance or neural activation. To this end, both the sgACC and the amygdala have been suggested as potential 'biomarkers' of treatment response in depression (Dunlop and Mayberg, 2014; Fu et al., 2013). However, many patients may still not respond. In patients who do not respond, or who respond only minimally, the search for novel treatments and ways to augment current treatments is essential. Thus, a second direction could be to develop novel brain circuit-based treatment options that directly target these circuits implicated in depression.

1.4 Targeted brain stimulation in depression

Antidepressant medication, CBT, and ECT can in many cases be highly effective. Although medication and CBT are less invasive, neither – along with ECT – were developed to target specific neural mechanisms of depression (although they do produce specific effects with respect to brain circuitry). If the neural basis of depressed mood is really centred on particular neural loci and circuits, which are

indirectly altered by these more global depression interventions, it may be more effective to alter activity in particular neural loci using a targeted approach. This approach might also be able to improve symptoms not usually affected by typical treatments but with specific neural correlates (such as the DLPFC in cognitive control), or, indeed, target patients who do not respond to other interventions.

Several techniques to directly stimulate the brain in a targeted manner have arisen. In general, neurostimulation tends to allow more specific targeting than antidepressant drugs, CBT, and ECT, though brain stimulation techniques differ widely in their specificity and relative invasiveness (see Figure 1.2). These techniques fall broadly into three categories: deep brain stimulation (DBS), which has high specificity but is also highly invasive; transcranial magnetic stimulation (TMS), which has moderate specificity and low invasiveness; and noninvasive electrical stimulation (most commonly, transcranial direct current stimulation, tDCS), which has moderate specificity (though lower than TMS) and low invasiveness. In addition, although it has a poor reputation among the general public, ablative brain surgery is (infrequently) used in depression, and seems to show similar efficacy to DBS (Volpini et al., 2017).

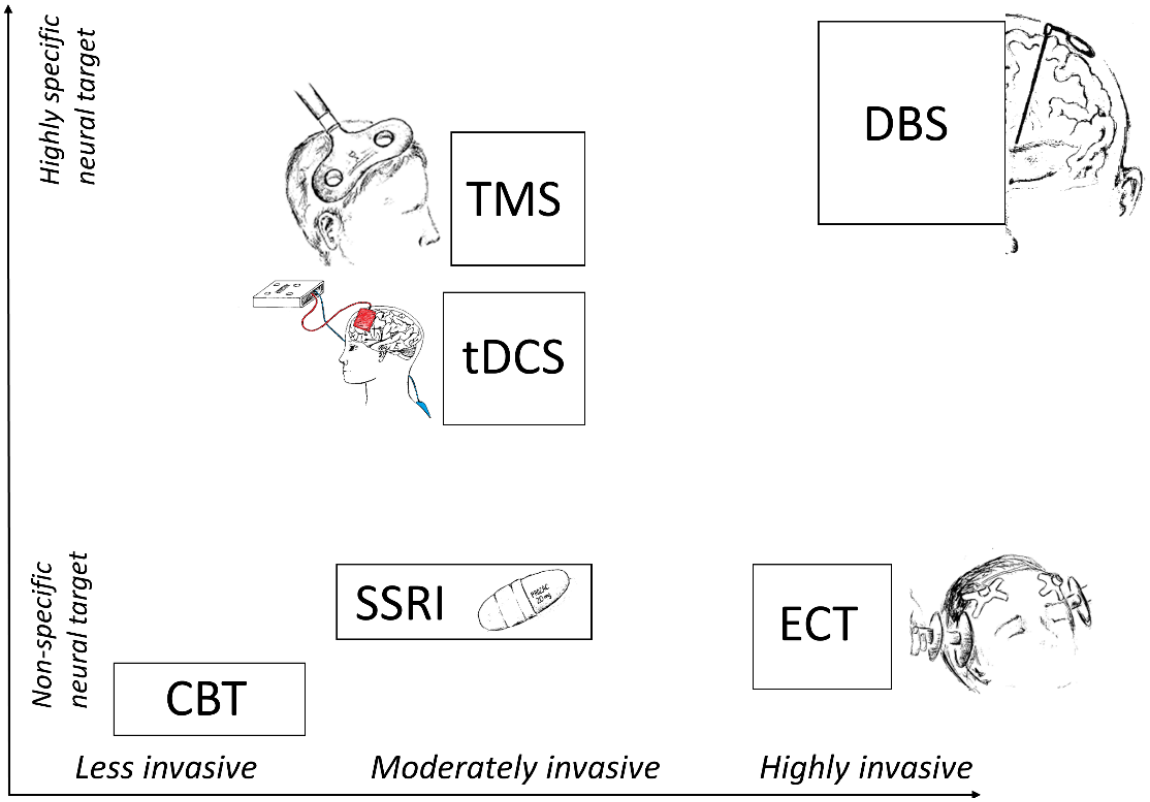

Figure 1.2 Treatment options for depression. Schematic of relative invasiveness (horizontal axis) and specificity of targeting (vertical axis) of six treatment options for depression. CBT=cognitive behavioural therapy; SSRI=selective serotonin reuptake inhibitor; ECT=electroconvulsive therapy (ECT); TMS=transcranial magnetic stimulation (TMS); tDCS=transcranial electrical current stimulation.

1.4.1 Deep brain stimulation

The discovery of deep brain stimulation in depression arose as a result of advancements in treating another brain disorder, Parkinson's disease (PD). Like depression, PD alters a distributed neural system due to loss of dopamine transmission. In PD, impairments initiating movements and pathological tremor originate from destabilisation of dynamic fronto-striatal-thalamic loops (Obeso et al., 2017). PD is initially treated with a global intervention: the medication levodopa increases the availability of dopamine in the brain, alleviating disabling motor symptoms caused by the death of dopamine neurons in the substantial nigra (Lloyd et al., 1975). Unfortunately, after several years of treatment, levodopa ceases to be effective at lower doses, and higher doses produce debilitating side-effects in most

patients, in the form of involuntary movements called dyskinesias (Dauer and Przedborski, 2003). In the early 1990s, a group found that electrical stimulation of the thalamus could alleviate tremor in PD (and patients with essential tremor) (Benabid et al., 1991). Today, more than 100,000 patients with PD have been implanted with DBS electrodes, placed in locations known to be dysfunctional in PD (the subthalamic nucleus or the internal aspect of the globus pallidus are most common) (McIntyre et al., 2015). The discovery of DBS as an effective treatment for PD combined with emerging knowledge about the neural circuitry disrupted in depression spurred the field of psychiatry into developing similar targeted invasive electrical stimulation for psychiatric disorders.

In a seminal experiment by Mayberg and her colleagues, DBS electrodes were implanted in the sgACC in six patients with intractable depression (Mayberg et al., 2005). This work was built on the theoretical basis of the sgACC as a 'node' in depression circuitry, mediating both diminished activity in dorsal neocortical regions and increased activity in ventral paralimbic regions in depression (Mayberg, 2003). Of the six patients with intractable depression, four showed a striking and sustained remission of symptoms, as well as local and distal changes in neural metabolism (Mayberg et al., 2005). Before electrode implantation, depressed patients showed elevated blood flow in the sgACC, compared to healthy controls, as well as changes in other regions associated with depression, including decreased blood flow in the DLPFC. After DBS, patients who responded to DBS showed decreases in sgACC blood flow, and increased blood flow in the DLPFC (among other regions) (Mayberg et al., 2005). Therefore, DBS might directly restore normative activation in the sgACC itself (in responders), but additionally, via connections from the sgACC, exert widespread effects on a larger network, including in the DLPFC. In the context of the

cognitive neuropsychological model of depression, DBS may be interpreted as targeting negative biases directly, through its direct actions on the sgACC and interconnected regions involved in hot cognitive processing, including the amygdala. In support of this, one study found a reduction in negative self-bias following DBS (Hilimire et al., 2015). In contrast, DBS does not seems to directly improve cold cognition in depression (Bergfeld et al., 2017).

Since the initial report in 2005, a number of patients with severe depression have been treated with DBS (usually those who have not responded to any conventional treatment). Electrodes have been implanted in several different regions implicated in depression, including the nucleus accumbens, ventral striatum/ventral capsule, sgACC, lateral habenula, inferior thalamic nucleus, and the medial forebrain bundle (Morishita et al., 2014). However, RCTs adhering to sham-controlled designs (the gold standard for clinical efficacy) have reported mixed results. Among these, only one RCT has reported clinical efficacy of active DBS (in the anterior limb of the internal capsule) over sham DBS (Bergfeld et al., 2016). Interestngly, this study found no improvement (even practice effects) in cold cognition following DBS (Bergfeld et al., 2017). Other randomized sham-controlled trials have produced negative findings (Dougherty et al., 2015), or failed a futility analysis (Morishita et al., 2014; Schlaepfer, 2015). Many methodological factors have likely contributed to these negative outcomes, including specific stimulation parameters (time at which stimulation begins; selection of sham condition DBS target) (Schlaepfer, 2015). In future, DBS trials may be improved by more individualised protocols; for example, using white matter tractography to identify individually-optimised electrode locations (Riva-Posse et al., 2014).

1.4.2 Transcranial magnetic stimulation

One of the best-known forms of noninvasive brain stimulation is transcranial magnetic stimulation (TMS). TMS uses brief, high-current pulses to induce a magnetic field, generating an electric field perpendicular to the magnetic field, and indirectly activates corticospinal neurons through synaptic inputs (Hallett, 2000). High-frequency repetitive TMS (rTMS), the form most commonly used in depression, can produce long-lasting effects on cortical excitability (by contrast, low-frequency rTMS can decrease cortical excitability), potentially due to effect on neural long-term potentiation and depression (Hallett, 2000).

Unlike DBS, TMS (and other forms of noninvasive brain stimulation) are limited in that they target primarily superficial regions of the brain. Direct targeting of the deeper structures is challenging (although there are some claims along these lines, e.g. sgACC modulation via rTMS of the supplementary motor area (Vanneste et al., 2014)). In depression, high-frequency rTMS has typically been used to target the left DLPFC (George et al., 1995). Several large randomized sham-controlled trials have shown clear antidepressant effects of daily left prefrontal rTMS over sham stimulation (Loo and Mitchell, 2005; O'Reardon et al., 2007). Based on these results, rTMS of the left DLPFC has been approved as an alternative treatment option for patients with treatment-resistant depression since 2008 by the US Food and Drug Administration, and since 2015 by the UK National Institute for Health and Care Excellence.

Clinical response to rTMS seems to depend on both frontal and subcortical mechanisms. Behaviourally, rTMS of the DLPFC has been reported to result in improvements in cognitive control (Martis et al., 2003), unlike other treatments for

depression. Even a single rTMS session, which is insufficient to cause mood improvement, can improve attentional control; this improvement has been shown to predict subsequent response to rTMS treatment (Vanderhasselt et al., 2009). However, a single rTMS session is also reported to attenuate amygdala activation during negative emotion processing (Baeken et al., 2010). An early clinical trial found that rTMS responders showed higher inferior frontal lobe metabolism at baseline, compared to nonresponders (measured using single photon emission computed tomography: SPECT); following 10 days of rTMS treatment, there was an even greater difference in inferior frontal lobe metabolism between responders and nonresponders (Teneback et al., 1999). More recently, a PET study found that nonresponders in an RCT of TMS showed heightened left amygdala activation at baseline, compared to responders (Martinot et al., 2011). These results accord with the predictions of the cognitive neuropsychological model of depression: that TMS may target cold top-down processing, with attendant possible indirect effects on low-level hot cognitive processing (Roiser and Sahakian, 2013).

However, there are some important drawbacks of rTMS treatment for depression. High-frequency rTMS has the potential to cause seizures, even in those without a history of seizures, though this is extremely rare (Hallett, 2000). Additionally, placebo (sham) blinding of studies is difficult. There are two commonly-used options for sham TMS: tilting the coil such that cortical stimulation is reduced but scalp sensation is preserved, which itself may cause low levels of cortical stimulation (Loo et al., 2000), or delivering low or no stimulation, where subject blinding may be ineffective (Loo and Mitchell, 2005). This complicates interpretations of effect sizes both within the rTMS field and when comparing rTMS to other interventions. Indeed, differences in stimulation parameters for both active and sham treatment arms likely contributes to

the substantial heterogeneity between different rTMS trials for depression (Loo and Mitchell, 2005).

1.4.3 Transcranial direct current stimulation

The second main form of noninvasive brain stimulation that has been suggested as a treatment for depression is transcranial direct current stimulation (tDCS), again predominantly over the DLPFC (Nord and Roiser, 2015). The practical advantages of tDCS (in comparison to rTMS and DBS) are many: tDCS is comparatively inexpensive, portable, and safe. Very few serious side effects have been reported in any tDCS trials for depression (in contrast to the potential for induction of seizures from rTMS (Hallett, 2000)). The most common side effects from DLPFC tDCS include temporary itching, tingling, or skin redness, and very limited reports of hypomania (Brunoni et al., 2013; Loo et al., 2012). In common with other brain stimulation therapies, tDCS has the advantage over medication and CBT that it can directly target putative neural circuit abnormalities in depression, though arguably with less specificity than rTMS and DBS since the current is much more diffuse. Nevertheless, it provides another means of directly altering an established neural correlate of depression.

As with rTMS, in the context of the cognitive neuropsychological model, tDCS could be predicted to improve cognitive control and enhance regulation over limbic areas in depression (Disner et al., 2011). The idea that tDCS might improve cognitive control in depression is based in part on the well-described ability of tDCS to improve performance in tasks involving cognitive control, such as working memory, which tDCS has been reported to enhance in healthy individuals (Fregni et al., 2005; Lally et al., 2013) as well as depressed patients (Oliveira et al., 2013). A number of other

improvements seen under tDCS – for example in selective attention (Gladwin et al., 2012) and planning (Dockery et al., 2009) – indicate that it may have particular capacity to treat cold cognitive impairment in depression. However, it is unclear if corresponding neural changes (i.e., in the DLPFC) underpin any effects on depressive symptoms, as only a small number of RCTs have been conducted, none of which used PET or fMRI to assess the mechanistic changes accompanying treatment. In addition, there is some scepticism as to whether the effects of tDCS on cold cognitive function are robust (Horvath et al., 2015).

It is also possible that tDCS has indirect effects on low-level hot cognitive processing through distal effects on subcortical regions: one study found that DLPFC tDCS evoked an anxiolytic-like effect on threat vigilance in healthy volunteers, although tDCS did not change performance on other emotion processing tasks typically affected by antidepressant drug treatment (Ironside et al., 2015). Although few such studies have been conducted, this suggests that DLPFC tDCS may directly alter cold cognitive processing, but possibly also indirectly affect negative biases, for example through improving attentional control over threatening stimuli. However, this hypothesis has not yet been tested in depressed patients.

In the next section, I will discuss the basis of tDCS as a treatment for depression. First, I will outline its historical use, its resurgence in modern years, and current theoretical advances in understanding its mechanism. Then, I will discuss research supporting the use of DLPFC tDCS in depression, and outline the major obstacles to making tDCS clinically useful on a large scale, in particular the need for experimental work to clarify the cognitive and neural mechanisms of depression it targets. Finally, I will attempt to integrate the antidepressant effects of DLPFC tDCS into the cognitive

neuropsychological model of depression, hypothesizing that it may improve cognitive control, and thereby improve top-down regulation of responses to negative emotional information. This will then form one of the central hypotheses tested in the experimental work in this thesis.

1.4.3.1 tDCS as an historical treatment for depression

Transcranial direct current stimulation is often cited as a "new noninvasive neurostimulation treatment" (Brunelin et al., 2012; Steinberg, 2013). Per contra, the use of electrical currents to excite the brain in the service of clinical intervention has a very long history: in ancient Mesopotamia, Scribonius Largus described the use of electrical torpedo fish to produce pain and headache relief (Largus and Bernhold, 1786). More recent neurostimulation treatments appeared around the turn of the 19th century, when Giovanni Aldini conducted a series of experiments applying electric current to animal and human bodies, becoming famous for corpse 'reanimations' (Aldini, 1804; Parent, 2004). These studies led him to test galvanic stimulation as a treatment for various psychiatric disorders, employing transcranial direct electric current to cure a patient hospitalized with major depression ("melancholy madness") (Aldini, 1804).

The first studies of electrical stimulation on larger groups of psychiatric patients emerged in the late 19th century, conducted by psychiatrists Rudolph Gottfried Arndt (Arndt, 1870) and Wilhelm Tigges (Tigges, 1883). Tigges distinguished patients suffering from depression (for whom he concluded that electrical brain stimulation was reasonably effective when conventional therapy could no longer help) from patients with psychosis, whose delusions and hallucinations showed little response to brain stimulation (Steinberg, 2013; Tigges, 1883). Following these accounts,

electrotherapeutic clinics became commonplace across Europe; spas and seaside resorts frequently offered such facilities (Steinberg, 2011).

In the 1890s, criticism against the neurostimulation movement began, spurred in a large part by German neurologist Paul Julius Mobius, who had observed a large degree of variability in response to electrotherapy, and postulated that the effects of electricity may be entirely suggestive in nature (Mobius, 1891; Steinberg, 2011). Thereafter, direct electric current as a psychiatric therapy fell out of favour (although other types of electrotherapy, in particularly early forms of ECT, soon replaced it).

1.4.3.2 Modern tDCS research

Over the past 20 years there has been a resurgence of interest in tDCS, both as an experimental and clinical technique. This arose from an influential study in healthy humans (Nitsche and Paulus, 2000). In the mid-20th century, studies had reported a mood-enhancing effect of 'brain polarisation' (i.e. direct current stimulation) in depressed patients (Costain et al., 1964; Ramsay and Schlagenhauf, 1966; Redfearn et al., 1964). In one double-blind trial in 24 depressed patients, there was a significant improvement during a two-week period of stimulation, but not during two weeks of placebo stimulation (here the montage involved two anodal electrodes, one over each eyebrow, and the cathodal on the left leg) (Costain et al., 1964). However, for the most part, 20th century tDCS was primarily used in animal research (Bindman et al., 1962; Creutzfeldt et al., 1962; Eccles et al., 1962; Purpura and McMurtry, 1965; Terzuolo and Bullock, 1956), or in the context of invasive pre-surgical epilepsy diagnostics, where surface stimulation of about 1.5mA induces intracranial currents (Dymond et al., 1975).

In the first study to apply modern tDCS methods noninvasively in humans, Nitsche and Paulus (2000) used a battery-driven stimulator emitting 1 mA of anodal direct current to stimulate the motor cortex (with the cathodal electrode positioned on the contralateral orbit). They recorded excitability in the motor cortex using TMS motor evoked potentials at baseline and after short phases of anodal or cathodal tDCS. tDCS induced a significant increase in motor-cortical excitability (about 20%) during anodal stimulation, and a similar significant decrease during cathodal stimulation. This finding – that cerebral excitability is diminished by cathodal stimulation, but increased by anodal stimulation – has become a central tenet of tDCS research.

1.4.3.3 Physiological mechanisms of tDCS

All electrical brain stimulation capitalizes on the inherent electrochemical properties of neuron membranes (Hodgkin and Huxley, 1952). tDCS uses a weak electric current to stimulate a localized area of the brain ('direct' indicates that the current flows in a single direction, in contrast to 'alternating' current stimulation). The earlier term "polarisation" refers to the effects of tDCS on neuronal resting membrane potentials (Bishop and O'Leary, 1950). This effect is polarity-specific: anodal tDCS decreases the resting membrane potential of the neuronal soma, increasing the likelihood of depolarization, whereas cathodal tDCS raises the membrane potential of the soma towards hyperpolarization (Wachter et al., 2011) (see Figure 1.3 insert).

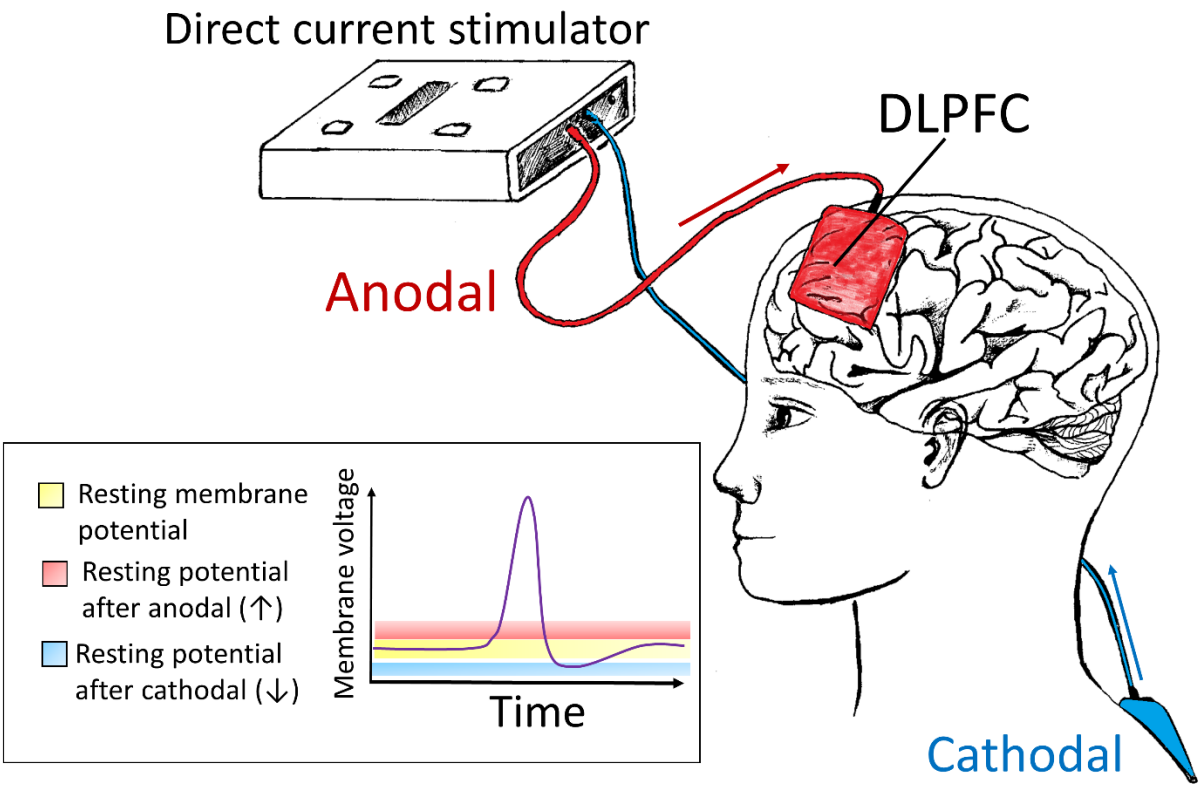

Figure 1.3 Diagram of a typical tDCS setup for depression. The anodal electrode is placed over the left DLPFC (red) and cathodal electrode over the ipsilateral shoulder (blue). Note the direction of current towards the electrode in the case of anodal stimulation, and away from the electrode in the case of cathodal stimulation. Insert: schematic illustration of neuronal resting membrane potential without tDCS, and after anodal (red) and cathodal (blue) tDCS. Figure adapted from Nord & Roiser (2015), *Advances in Clinical Neuroscience and Rehabilitation*.

In cognitive research, the most common placement of the anodal electrode is over the left DLPFC, in theory to improve its excitability (as anodal tDCS does to the motor cortex). Note, however, that the tDCS current is relatively diffuse, compared to the spatial specificity of TMS and certainly of DBS. Despite this, tDCS of the DLPFC has been reported to produce marked behavioural effects (usually improvements) in a diverse set of cognitive processes, including working memory (Andrews et al., 2011; Fregni et al., 2005; Hoy et al., 2013; Lally et al., 2013; Zaehle et al., 2011), mind-wandering (Axelrod et al., 2015; Kajimura and Nomura, 2015), and mood (Boggio et al., 2008; Brunoni et al., 2013; Fregni et al., 2006a; Loo et al., 2012; Martin et al., 2011), both during and after stimulation (known as ‘online’ and ‘offline’

stimulation protocols, respectively). The cathodal electrode varies in placement: it is often positioned supraorbitally (Lally et al., 2013) or over the ipsilateral deltoid (see Figure 1.3 for a diagram of a typical tDCS for depression set-up); a bifrontal monage, with the cathodal electrode over the right DLPFC, is also sometimes employed (Brunoni et al., 2017). In all instances, this creates an electrical circuit with current travelling from the anodal (positive) to the cathodal (negative) electrode. Montages for tDCS treatment of depression usually use current of between 1 and 2 mA, which delivers low levels of electrical stimulation through the skull immediately under the anode, with a small proportion (~10%) penetrating to the cortex beneath. This stimulation has the capacity to facilitate (but not directly evoke) neuronal activity. However, the precise mechanisms of tDCS are not fully understood.

The measurable behavioural changes during and after DLPFC tDCS are attributed to alterations in the membrane potential due to the passage of direct current. The usual interpretation is that depolarization produces an increase in the frequency of nerve impulses discharged, while hyperpolarization decreases the rate of discharge (Bindman et al., 1962; Lippold et al., 1960). This is difficult to test directly in humans, but one study investigating the neurophysiology of DLPFC tDCS did find evidence consistent with such an explanation, with a polarity-specific effect on both working memory performance and EEG measures: anodal tDCS improved behavioural performance and its electrophysiological correlates, while cathodal stimulation decreased both measures (Zaehle et al., 2011). In currently-depressed patients, DLPFC tDCS was reported to induce neurophysiological changes extending over the medial frontal cortex during working memory performance (Powell et al., 2014).

Most explanations for the cognitive effects of DLPFC tDCS rely strongly on the assumption that anodal current induces cortical excitability, while cathodal current induces inhibition. However, this assumes that tDCS will have the same effect on the DLPFC as it has on the motor cortex (Nitsche and Paulus, 2000). In reality, the effect of current depends heavily on local neuroanatomy: varying the location can elicit opposite effects, even within the same cortical layers (Purpura and McMurtry, 1965). Indeed, a mild anodal current can sometimes even inhibit neuronal activity (Priori et al., 1998). Furthermore, tDCS induces widespread neural changes (i.e. away from the stimulation site), as well as local non-neuronal effects, including local changes in ionic concentrations, levels of cyclic adenosine monophosphate, protein synthesis, and N-methyl-D-aspartate receptor efficacy (Arul-Anandam and Loo, 2009; Zaehle et al., 2011), all of which alter its local cortical effects. Thus the physiological basis of DLPFC tDCS may be much more complex than simply increased excitability.

1.4.3.4 Explaining the behavioural effect of DLPFC tDCS

It is perhaps unsurprising, then, that the behavioural effects of DLPFC tDCS also seem more complex than one would expect simply from local effects on DLPFC excitability. tDCS does have local effects on DLPFC activation, but it also seems to cause distal changes, including in regions more closely involved in hot cognitive processing such as the rostral ACC and OFC (Weber et al., 2014). tDCS also increases coupling between the left DLPFC and primary sensorimotor cortices, and decreases coupling between the DLPFC and bilateral thalami (Stagg et al., 2013), potentially driving the more complex behavioural effects of tDCS.

Several theoretical models have proposed potential mechanisms that might explain the behavioural effects of tDCS (in particular over the DLPFC). Three in particular

have gained prominence: excitation/inhibition balance models, zero-sum models, and input-selectivity models. Excitation/inhibition balance models propose that tDCS instates an optimal excitation/inhibition balance in the region stimulated (Krause et al., 2013). These models hypothesize that tDCS can be used to artificially modulate excitation/inhibition to optimise task performance, as well as in disorders with purported regional excitation/inhibition imbalances (such as autism (Rubenstein and Merzenich, 2003)). However, neural circuit models have demonstrated that shifts in the excitation/inhibition balance only alter speed-accuracy trade-offs (Wang et al., 2013). This finding may more closely support the next class of models, zero-sum models, which predict that performance enhancements via tDCS are always balanced by costs elsewhere (i.e., the net change in function is always zero) (Luber, 2014). The prospect of potential behavioural costs of tDCS is rarely discussed but is certainly important, especially in the context of possible risks of experimental clinical treatments (Bestmann et al., 2015; Luber, 2014). A third class of model, activity- or input-selectivity models, does not claim that tDCS is always a zero-sum intervention. Instead, it theorises that tDCS specifically enhances the function of already-active networks in the brain (Bestmann et al., 2015). This is supported behaviourally by evidence that combining tDCS of the DLPFC with a DLPFC-dependent task (the n-back task) results in greater performance benefits than tDCS alone (Andrews et al., 2011). Still, all three classes of models provide only a heuristic, conceptual understanding of what tDCS might do. This is problematic: there is an explanatory gap between understanding the effect of tDCS on local and distal physiology, and understanding its effect on behaviour.

This gap in understanding probably contributes to the substantial variability in the behavioural effects of tDCS reported in experimental studies. After initial studies

showed cognitive enhancement resulting from DLPFC tDCS, criticism began to emerge, particularly because the behavioural outcome of DLPFC tDCS varies substantially between studies. Between-experiment differences in protocol (e.g. placement of 'ground' electrode, size/shape of electrodes, use of electrode gel versus saline sponges, etc.) and inter-individual differences in anatomy and physiology (Tremblay et al., 2014) contribute to highly variable outcomes and behavioural results that have proven difficult to replicate. Notably, a recent widely-reported meta-analysis claimed to find no effect of single-session tDCS in healthy subjects on 42 different cognitive outcomes (Horvath et al., 2015). Several substantial issues have since been raised with the methodology of this meta-analysis, including inconsistent data selection methods and underpowered comparisons (Price and Hamilton, 2015). Nevertheless, it is essential to consider individual differences in response to tDCS. In future, tDCS studies might employ physiological measures (as well as already-existing software that accounts for anatomical variability) to guide stimulation parameters. This could be particularly useful when refining DLPFC tDCS parameters to best address a relatively heterogeneous disorder such as depression.

1.4.3.5 Clinical trials of tDCS in depression

The first double-blind, sham-controlled RCT of tDCS for depression reported very pronounced effects of tDCS on mood symptoms (Fregni et al., 2006a) after twenty minutes of stimulation. Differences between active and sham (placebo) tDCS even persisted over the succeeding month. Less marked (but nonetheless substantial) effects of tDCS were later reported in a three-week trial: tDCS improved mood significantly more than sham, but no difference between active and sham was found

in response rates (Loo et al., 2012). Cognitive effects were also smaller than reported in previous trials, with attention and working memory improvements found after the first tDCS session, but no cumulative cognitive enhancements independent of mood effects.

One RCT tested a combination of DLPFC tDCS and an SSRI (sertraline), reporting that combined tDCS-SSRI treatment was more effective than either treatment alone (Brunoni et al., 2013). Although this work also suggested that tDCS had a similar effect size to antidepressant medication, a more recent RCT failed to show noninferiority of tDCS to the SSRI escitalopram (though both were statistically superior to sham tDCS combined with placebo) (Brunoni et al., 2017). This inconsistency is less surprising in the context of the widely variable effect of tDCS on depression symptoms throughout the literature: some studies find substantially larger effect sizes than others; others fail to show an effect of tDCS on depression symptoms at all (see Figure 1.4) (Shiozawa et al., 2014).

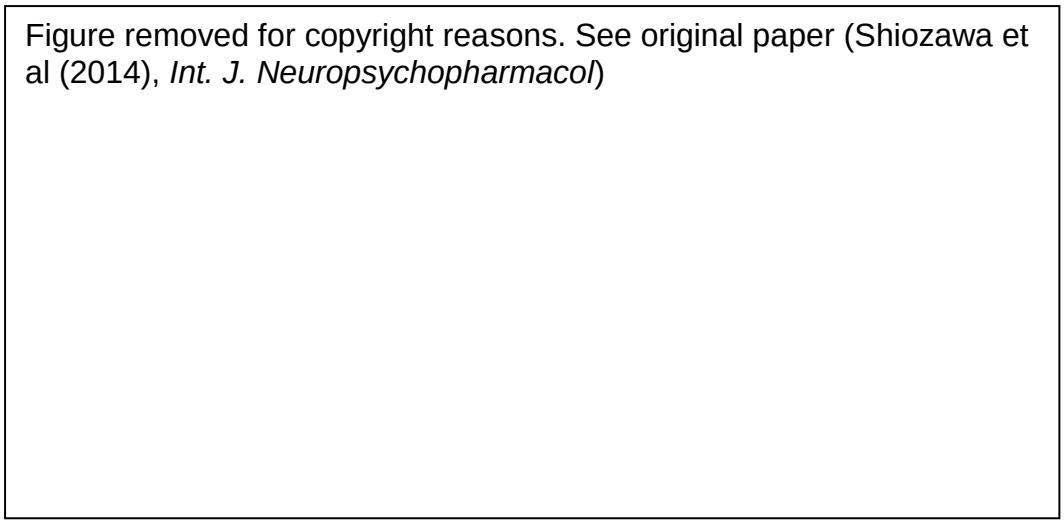

Figure 1.4 tDCS trials in MDD. Forest plot of effect sizes (Hedges' g) to illustrate the relative strength of treatment effects for each selected study, including the overall effect (vertical line), the standardised mean difference (SMD), and confidence interval (CI). Figure reproduced from Shiozawa et al (2014), *Int. J. Neuropsychopharmacol.*

As with behavioural studies, differences in stimulation parameters, outcome measures, and timing of tDCS delivery could all account for variation in its effectiveness at treating depression. A meta-analysis of individual patient data from clinical trials of tDCS in depression identified several contributors to tDCS efficacy, most notably stimulation dose (number of sessions and amount of current delivered) (Brunoni et al., 2016). Interestingly, the trial that failed to show non-inferiority of tDCS relative to escitalopram employed an unusually high dose of tDCS (22 sessions at 2 mA). Clearly, the optimal schedule for tDCS intervention in depression still requires clarification.

From a pragmatic perspective, tDCS has great potential as a safe non-invasive brain stimulation treatment for depression. However, its effectiveness is still in question. To date, most research on tDCS for depression has adopted one of two strategies: RCTs to determine whether tDCS improves depressive symptoms; or experimental studies, usually in healthy subjects, to determine its mechanism of effect. This division obscures a better understanding of the specific mechanisms driving the

antidepressant effects of tDCS. Studies combining both strategies have the ability to resolve this, and determine how tDCS may target symptoms of depression.

A small number of studies have introduced mechanistic measures to tDCS RCTs, which begin to answer this question. For example, baseline cortical inhibition in tests of motor-cortex excitability (measured using motor-evoked potentials) was associated with worse response to tDCS (but also to escitalopram; thus the predictor was not treatment-specific) (Brunoni et al., 2017)). However, to date, no RCT of tDCS in depression has included neuroimaging measures to assess the neural effects of this intervention. Such a design would also be extremely useful in identifying potential 'biomarkers' of tDCS response. As with other treatment-specific predictors, it could have potential use in patient selection; and because tDCS is an experimental treatment, it would also provide invaluable mechanistic insight.

1.5 Thesis aims, hypotheses, and predictions

The overall aim of this thesis was to investigate the role of DLPFC dysfunction in depression, and whether this impairment could be targeted with noninvasive brain stimulation. This aim emerges from two separate lines of research. First, it draws on the predictions of the cognitive neuropsychological model of depression in testing whether cold cognitive processing (and DLPFC function) may promote resilience to and recovery from depression, in unaffected at-risk populations and in patients who are receiving an intervention. It also emerges from clinical brain stimulation research indicating that the DLPFC can be targeted noninvasively with tDCS, and that this targeting may improve mood in depression. Because these lines of research have rarely been explored in tandem, the neural and cognitive mechanisms of DLPFC

tDCS in depression are still extremely unclear, obscuring how these processes might best be harnessed in a clinical setting. Therefore, I set out to investigate the cognitive and neural mechanisms of DLPFC tDCS as a treatment for depression, testing whether DLPFC tDCS affects hot and cold cognitive processing, whether DLPFC activation is related to risk for depression, and, lastly, whether DLPFC tDCS would augment the efficacy of CBT in a randomized, sham-controlled clinical trial. Chapter 2 provides a brief overview of some of the common methodological approaches used in the thesis. Chapter 7 provides a general discussion of the results of each of the experimental chapters and attempts to draw some conclusions across the different chapters. The content of the experimental chapters (Chapters 3-6) of the thesis is as follows:

Chapter 3

Chapter 3 investigates the cognitive mechanisms of DLPFC tDCS in healthy volunteers, during a single stimulation session with parameters similar to those used in RCTs for depression. The aim was to test whether DLPFC tDCS acutely modulates hot emotional processing biases, in a manner similar to the acute effect of antidepressant drugs. I test this using an emotion identification task, where faces are morphed along a continuum from an extreme emotion (e.g. anger) to a neutral face. Participants identified facial emotions during active or sham tDCS of the left DLPFC. I hypothesised that tDCS would modulate hot cognitive processing by eliciting a positive bias (in accuracy or reaction time) in emotional face identification.

Chapter 4

In Chapter 4 my aim was to clarify the neural mechanisms involved in hot and cold cognition in three populations: healthy controls, currently-depressed patients, and individuals at risk for depression (unaffected first-degree relatives of depressed patients). To this end, I measured DLPFC activation (using fMRI) during working memory, and sgACC and amygdala activation during emotion processing. I intended to test two specific predictions arising from the cognitive neuropsychological model of depression: that DLPFC activation during cold cognitive processing would be preserved in the unaffected relatives of depressed patients, compared to patients currently experiencing symptoms; and that amygdala and sgACC activation during emotion identification would be negatively biased in both at-risk and currently depressed groups. In particular, evidence of preserved DLPFC activation in the unaffected relatives group could potentially indicate a neural mechanism of resilience that could be harnessed as a possible target of interventions in depression.

Chapter 5

In Chapter 5, I report the results of a double-blind RCT to test whether anodal tDCS of the left DLPFC augments the effects of CBT for depression. The primary outcome measure was clinical response, measured with the Hamilton Rating Scale for Depression (HAM-D). At the time of writing, this was the first RCT to combine tDCS with CBT, and was also unusual in measuring neural activation during hot and cold cognitive processing at baseline and post-intervention with fMRI (in addition to more typical symptom and cognitive measures). We hoped not only to test a novel intervention for depression, but also to characterise the mechanism driving any effects. I expected the group receiving anodal tDCS (and CBT) to show a greater

reduction in depression symptoms than those receiving sham tDCS (and CBT), and that this difference would be accompanied by improvements in working memory and increases in DLPFC activation.

Chapter 6

In Chapter 6, I sought to uncover whether any variables collected at baseline accurately predicted clinical response in the RCT reported in the previous chapter. To this end, I tested how well symptom, cognitive, and neural measures predicted change in our primary outcome measure, the HAM-D. I tested which baseline variables predicted clinical response specifically to active tDCS, as well as general response to CBT (irrespective of tDCS group). I had two primary hypotheses: that activation at baseline in the left DLPFC would predict response to tDCS specifically (a prospect that has never been explored in previous work); and that, as reported in previous studies, amygdala activation would generally predict response to CBT, independent of active or sham stimulation.

Chapter 2. Experimental Methods

This chapter will describe the materials and methods common throughout the experimental chapters of this thesis. I will describe the psychiatric screening procedures and self-report questionnaires used in Chapters 4 through 6, and the tDCS parameters common to Chapters 3, 5, and 6. I will also describe two types of cognitive paradigms: emotional face tasks, used in all chapters, and the working memory n-back task, used in Chapters 4 through 6.

2.1 Montreal International Neuropsychiatric Interview

For the studies presented in Chapter 4, 5, and 6, all participants were screened using the Mini International Neuropsychiatric Interview (MINI, Sheehan et al., 1998). This screening interview is used to assess presence or history of psychiatric illness for clinical trials and other research studies. The MINI consists of a structured diagnostic interview in accordance with the Diagnostic and Statistical Manual of Mental Disorder-IV (DSM-IV). We employed a condensed version of the MINI, comprising 12 of the original 16 subsections, assessing presence and history of a major depressive episode, a (hypo) manic episode, panic disorder, agoraphobia, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), alcohol abuse and dependence, non-alcohol psychoactive substance use disorders, psychotic disorders (including mood disorder with psychotic features), anorexia nervosa (both restrictive and binge-purge subtypes), bulimia nervosa, and generalized anxiety disorder. The sections not included in the condensed version were: dysthymia, suicidality, social phobia, and antisocial personality disorder.

Separately, a structured suicide risk assessment procedure was employed in any patients reporting thoughts of death or self-harm.

Healthy volunteers and unaffected first-degree relatives of depressed patients (Chapter 4) were excluded if they met criteria for any current or previous psychiatric condition, as assessed by the MINI. Depressed patients (Chapters 4, 5, and 6) were included only if their current symptoms met criteria for a major depressive episode, but were excluded if they met criteria for a manic or hypomanic episode (past or current), or a psychotic episode (past or current), with the exception of those meeting criteria for a mood disorder with psychotic features. Current or previous substance use disorders, including alcohol, were excluded unless substance abuse/dependence was confined to previous depressive episodes. Other disorders, including panic disorder, agoraphobia, OCD, PTSD, anorexia and bulimia nervosa, and generalized anxiety disorder were not exclusion criteria for depressed patients, given the extremely high comorbidity between depression and these other conditions.

2.2 Self-report questionnaires and Weschler Test of Adult Reading

Even among healthy controls not meeting criteria for any psychiatric condition, mood and anxiety symptoms vary considerably between individuals. Specific symptoms and their severity also vary between depressed patients, and within the same patient at different times, particularly in the context of an RCT. For this reason, healthy controls and unaffected relatives of depressed patients completed three self-report questionnaires, measuring subjective mood, anxiety, and anhedonia, the inability to experience pleasure from normally-pleasurable activities (Chapter 4). These three

questionnaires were also completed by all depressed patients (Chapters 4, 5, and 6). In the case of the RCT (Chapters 5 and 6), these three questionnaires enabled us to track mood and anxiety within patients across nine assessment time points. The three questionnaires we administered were: the revised Beck Depression Inventory (BDI: Beck et al., 1996), the Beck Anxiety Inventory (BAI: Steer and Beck, 1997), and the Snaith-Hamilton Pleasure Scale (SHAPS: Snaith et al., 1995).

The BDI is a 21-item questionnaire in which participants are instructed to select from a group of four statements the statement that best describes how they have been feeling during the past few days. Each item consists of statements scored 0 to 3, with statements scoring 0 including “I do not feel sad” and “I do not feel like a failure”; statements scoring 1 including “I feel sad”; statements scoring 2 including “I am sad all the time and I can’t snap out of it”, and statements scoring 3 including “I am so sad or unhappy that I can’t stand it”. Each participant’s score is calculated by summing the scores for each question, and can range from 0 to 63; a score above 15 is typically considered clinically relevant (Sprinkle et al., 2002). The BDI has been shown to have high internal consistency for both psychiatric and nonpsychiatric populations (Beck et al., 1988).

The BAI is a 21-item self-report scale developed for the assessment of anxiety in psychiatric patients (Steer and Beck, 1997). The 21-items scale lists common anxiety symptoms, which have been found to load onto four factors: subjective symptoms of anxiety (e.g., “unsteady”), neurophysiological symptoms of anxiety (e.g., “numbness or tingling”), autonomic symptoms of anxiety (e.g., “indigestion”), and panic symptoms of anxiety (e.g., “fear of worst happening”) (Leyfer et al., 2006). Participants or patients are instructed to indicate how much they have been bothered

by that symptom during the past week, by circling the numbers corresponding to “Not at all” (0); “Mildly but it didn’t bother me much” (1); “Moderately – it wasn’t pleasant at times” (2); and “Severely – it bothered me a lot” (3). Summing these numeric scores, participants can fall anywhere on the scale of 0 to 21 (no to low anxiety) to 36 and above (high anxiety). The BAI has been shown to be highly internally consistent and acceptably reliable over 11 days in a sample of patients with anxiety disorders (Fydrich et al., 1992). The BAI also compares favourably with other common subjective measures of anxiety, such as the State-Trait Anxiety Inventory (STAI): BAI scores were found to be significantly less confounded with depression than STAI scores (Fydrich et al., 1992). Its high internal reliability makes it particularly suitable for within-subjects designs (e.g., tracking any anxiolytic effects of an intervention, Chapters 5 and 6), as well as for distinguishing anxious traits from depression in samples suffering from (or at risk of) depression (Chapters 4-6).

The SHAPS is a 14-item scale used to assess hedonic tone and its absence, anhedonia. Anhedonia is classically defined as a loss of the ability to experience pleasure (Snaith, 1993), though more recent definitions incorporate broader constructs of motivation, anticipation, and reward valuation (Der-Avakian and Markou, 2012). The scale comprises four domains of pleasure response: interests and pastimes, social interaction, sensory experience, and food or drink (Snaith et al., 1995). Each of the 14 items consists of a statement which the participants rate on a scale from “Definitely agree” (scored as 0), “Agree” (scored as 1), and “Disagree” (scored as 2), to “Strongly disagree” (scored as 3). Statements include: “I would enjoy my favourite television or radio programme”; “I would find pleasure in the scent of flowers of the smell of a fresh sea breeze or freshly baked bread”; and “I would enjoy a cup of tea or coffee or my favourite drink”. After a participant has rated every

question, his or her score is calculated by summing the scores to a total, ranging from 0 to 42. Age and sex have not been found to have any major effect on scores (Snaith et al., 1995).

In all studies except Chapter 3, participants were also administered the Weschler Test of Adult Reading (WTAR: Wechsler, 2001). This is an oral test of verbal intelligence, which we used to attempt to match the groups according to intelligence quotient (IQ) (Chapter 4) and confirm that two arms of the clinical trial were adequately matched (Chapter 5). Participants were instructed to read a list of 50 words aloud; the list is made up of (relatively) infrequently-used words ('perspicuity'; 'lugubrious'; 'hegemony'). Each correctly-read word scores the participant one point, and participants' final scores can be converted to an IQ score using standard score conversion tables and age. We did not administer the WTAR to any participant who was not fluent in English, and excluded these participants from all IQ analyses (non-native English speakers who were educated in English were administered the WTAR).

In Chapters 3 and 5 only, participants were administered the tDCS Adverse Effects Questionnaire (Brunoni et al., 2011). In Chapter 5, we administered this questionnaire in all patients at least once; in Chapter 3, we administered this questionnaire in only a subset of participants (N=45). This adverse effects questionnaire was developed following a systematic review and meta-analysis of tDCS clinical trials, proposed to improve systematic reporting of tDCS-related side-effects (Brunoni et al., 2011). It assesses ten commonly-reported side-effects of tDCS (headache, neck pain, scalp pain, tingling, itching, burning sensation, skin redness, sleepiness, trouble concentration, and acute mood change), plus space for

a specified ‘other’ adverse event. For each side-effect (including ‘other’), participants indiciate whether a symptom was absent, mild, moderate, or severe. If a symptom is present, participants also indicate whether they believe it is related to the stimulation (not at all; remotely possible; probable; definite). This questionnaire allowed us to examine whether side-effects differed between active and sham stimulation conditions, which may affect efficacy of blinding.

2.3 Hot cognitive measures (emotional face tasks)

A tendency to process negatively-valenced stimuli over positive stimuli has been reported in depression across many domains, including memory (Matt et al., 1992), reward processing (Pizzagalli et al., 2009) and attention (Gotlib and Joormann, 2010). In the perceptual domain, depressed patient show disrupted behavioural (reaction times; accuracy of emotion identification) and neural responses to emotional face stimuli (e.g., Joormann and Gotlib, 2006; Surguladze et al., 2005, 2010; Suslow et al., 2010). Emotional face tasks can take several forms, including explicit emotional identification (e.g., “respond only to sad faces” in a sequence of emotional faces), incidental emotional face tasks (e.g., “respond only to old faces” in a sequence of emotional faces), and implicitly-presented emotional face tasks (i.e., when the presentation of each face is of a duration below the participant’s threshold of perception). In this thesis, we employ the first two types of tasks.

In Chapter 3, I employ an explicit emotion identification task in the context of a behavioural tDCS study in healthy controls. In Chapters 4-6, I use an incidental emotion identification (gender identification) task in the fMRI scanner. Both are intended to probe disruptions in hot cognition in depression: in Chapter 3, measuring

emotion identification, and in Chapters 4-6, measuring neural reactivity to negative and positive emotional faces.

2.3.1 Explicit emotional face task

Depressed patients show a decreased sensitivity to positive facial expressions, compared to healthy controls during explicit emotion identification (i.e., a higher intensity of expression is needed for patients to correctly detect positive emotions) (Joormann and Gotlib, 2006). Conversely, patients show an increased sensitivity to sad facial expressions (Joormann and Gotlib, 2006).

In Chapter 3, I employed an explicit emotional face identification task sensitive to emotional biases (Bamford et al., 2015). This task is unusual in its employment of a prototypical emotional face, rather than the more typical neutral face. This has the advantage of making the comparison stimulus genuinely emotionally ambiguous. It also bears a closer resemblance to how visual representations are thought to be coded: with reference to a prototypical, not a neutral, face (Skinner and Benton, 2010).

The paradigm uses photographs from twelve young adult males with posed facial expressions (happy, sad, angry, disgusted, fearful, surprised, and neutral) (Bamford et al., 2015). Each face has been morphed along the axis of prototypical to each specific emotion using Active Shape Models (Tiddeman et al., 2001). The prototypical face is a composition of all 12 individuals' seven facial expressions (six emotions, and neutral). The final face stimuli used in the task comprise faces morphed along each axis of emotion intensity; for instance: a face 5% along the

dimension of prototypical to disgusted (95% prototypical), or a face that was 90% along the dimension of prototypical to angry (90% angry) (see Figure 2.1).

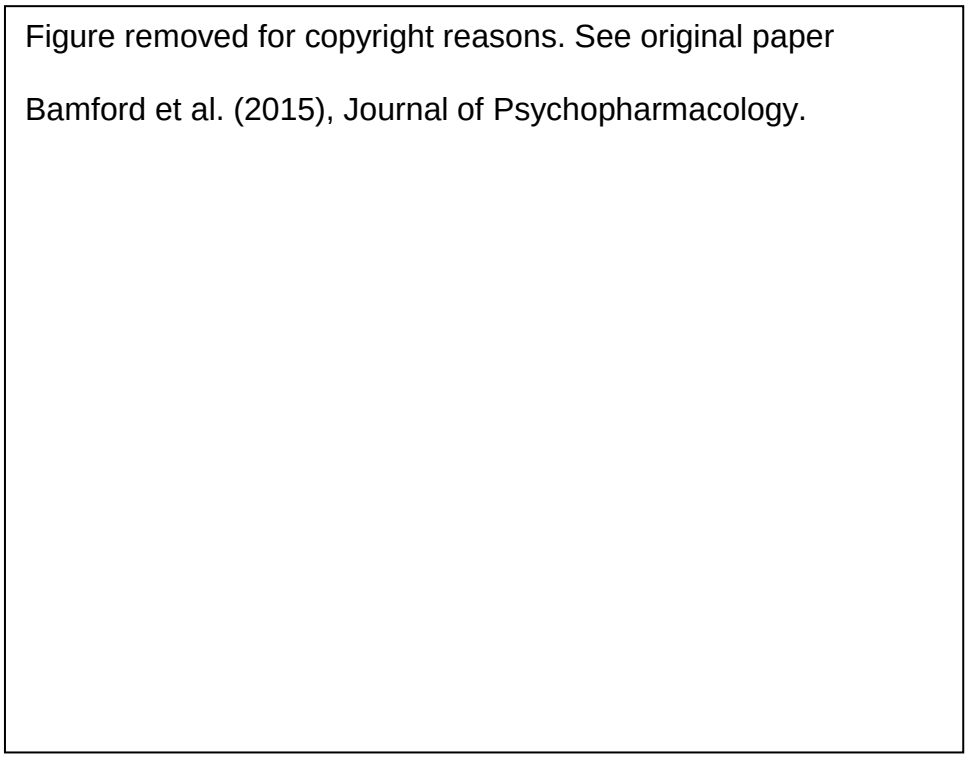

Figure 2.1 Axis of emotional expression. Centre represents morphed prototypical emotional face; outer circle represents maximum emotion expression. Emotions from centre top, clockwise: disgusted, happy, surprised, angry, sad, and fearful. Figure adapted from Bamford et al. (2015), *Journal of Psychopharmacology*.

2.3.2 Incidental emotional face task

Incidental emotional face tasks require participants to respond to non-emotional features of faces (e.g., gender; age), while manipulating the emotion of face stimuli (e.g., happy; fearful) to measure the effects of emotionality on behavioural or neural measures. When combined with neuroimaging techniques, incidental emotional face tasks have revealed exaggerated limbic responsivity to negative facial expressions in depression, a putative neural mechanism for negative bias (e.g., Surguladze et al., 2005, 2010). In Chapters 4-6, I use an incidental emotional face task where

participants were instructed to identify the gender of each face during blocks of happy, fearful, and neutral faces presented inside the MRI scanner (see Figure 2.2). Previously, this task has been found to evoke amygdala and subgenual anterior cingulate cortex (de)activation (O'Nions et al., 2011). In Chapter 4, we used this task to measure differences in limbic responsivity between depressed patients, healthy controls, and unaffected relatives of depressed patients. In Chapter 5, we used the same task to detect neural changes in emotion processing resulting from a clinical trial of tDCS and CBT, providing a measure of within-subject changes in limbic reactivity following clinical interventions. Lastly, we used the same task to uncover regions potentially predictive of clinical response to tDCS and psychotherapy in Chapter 6.

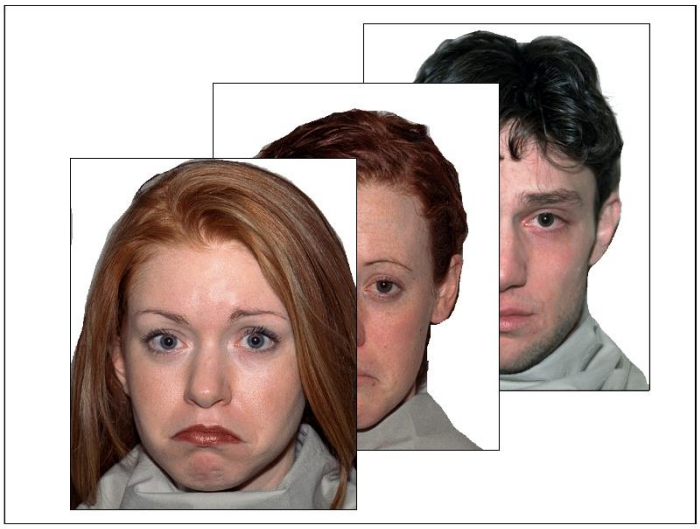

Figure 2.2 Incidental emotion processing task. Three example trials of a 'sad faces' block. Participants were not told to attend to the emotions of each face, and instead made speeded responses to classify each face's gender.

2.4 Cold cognitive measures (working memory and distractibility tasks)

In addition to emotional face tasks, we also employed measures of cold cognitive processing in all chapters of the thesis: the n-back task (Chapters 4-6) and the

distractibility task (Chapter 3). Both involve making speeded judgements that involve a relatively high working memory load (n-back task) or attentional load (distractibility task); ostensibly, neither involve any aspect of emotion processing. These tasks were used to assess non-emotional mechanisms affected by brain stimulation (Chapter 3, 5, and 6) or risk for depression (Chapter 4).

2.4.1 N-back task

The n-back task measures working memory, the cognitive system providing temporary storage and manipulation of information necessary to execute complex tasks (Baddeley, 1992). It is a paradigm frequently used to quantify individual differences in working memory, and predicts inter-individual differences in other higher cognitive functions, such as fluid intelligence (Jaeggi et al., 2010). The n-back task manipulates working memory load by varying the task to be performed while keeping the sensory stimulus constant (Conway et al., 2005), making it a useful, flexible measure of working memory.

Typically, the n-back task involves the successive presentation of stimuli (letters, numbers, words, pictures, etc.). Throughout this stream of stimuli, the participant is instructed to make a response when the stimulus on-screen matches the one N-back (see Figure 2.3). In a version with very light working memory load, the 1-back (N=1), participants respond every time the stimulus on the screen matched the previous stimulus. In a more difficult version, the 3-back (N=3), participants respond every time the on-screen stimulus matched the stimulus presented 3 stimuli ago (i.e., *a ; b ; c ; a* : the final *a* is a 3-back hit). In our version, we used four consonants easy to distinguish from one another: *f*, *p*, *k*, and *h*. Participants completed nine interspersed blocks of the 1-back, nine blocks of the 3-back, and nine short periods of fixation

(rest). By manipulating the value of N, we systematically varied processing load (and therefore difficulty).

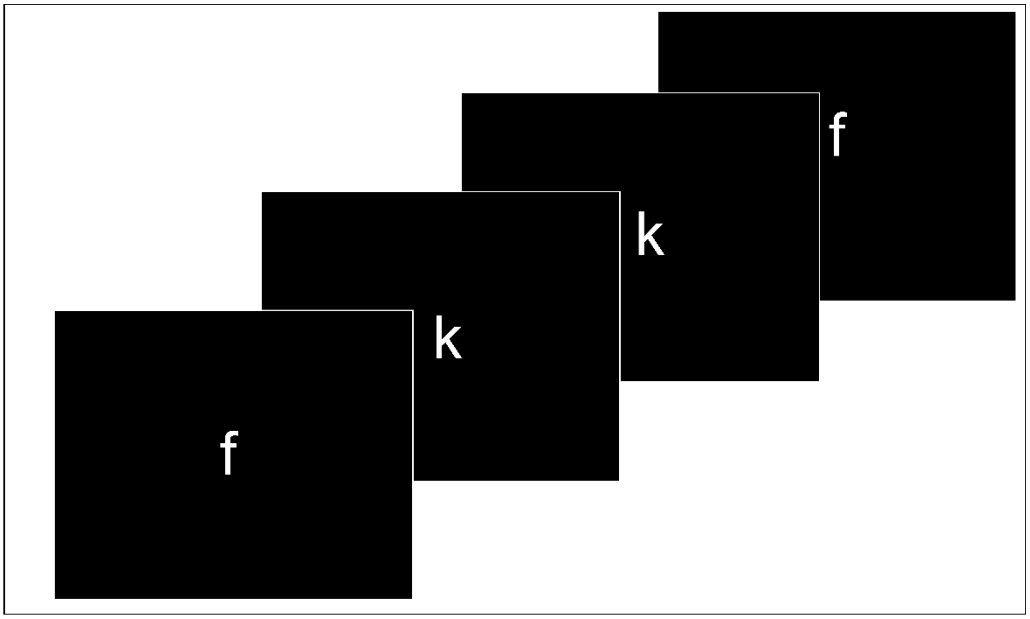

Figure 2.3 N-back task. Four example n-back trials. In the 3-back condition, the participant should respond to the fourth letter ('f'); in the 1-back condition, they should respond to the third letter ('k').

We calculate performance on the n-back task using d-prime (d'), defined as:

d'= Z(hit rate) – Z(false alarm rate)

where Z is the inverse of the cumulative Gaussian distribution. Hit rate is calculated as the proportion of correct button presses, and false alarm rate the proportion of incorrect button presses (i.e. the number of hits and false alarms, divided by the total number of opportunities for hits or false alarms, respectively).

In an imaging context, a design that parametrically manipulates load makes it possible to distinguish working memory-specific and non-specific neural activation (Chapters 4-6). This is particularly useful in studies with patient populations. In psychiatric disorders, including depression and schizophrenia, behavioural

performance on the n-back task is frequently impaired (Harvey et al., 2004; Krieger et al., 2005). The design of the n-back task makes it possible to measure the difference between neural responses to the high-load (3-back) and low-load (1-back) conditions, isolating the regions involved in load-sensitive (specific to working memory) processing from load-insensitive regions that perform other supportive functions, such as perception and action. Thus, specific deficits in the neural mechanisms of working memory in patients can be distinguished from more general deficits in motor responding, sensory processing, or other basic processes potentially disrupted by depression.

2.4.2 Distractibility task

In Chapter 3 only, I use an irrelevant-distractor paradigm to measure individual differences in attentional distractibility (see Figure 2.4). This paradigm was developed to measure the effect of task-irrelevant distractors on speeded behaviour (both task-relevant and irrelevant distractors interfere with performance, typically by slowing reaction times) (Forster and Lavie, 2008). The effect of task-irrelevant distractors on behaviour also correlates with self-reported mind wandering, indicating there is a general trait of susceptibility to both external and internal distractors (Forster and Lavie, 2014). Impairments in distractibility and failure to focus attention are commonly reported in patients with depression (Lemelin et al., 1997). The attention-distractibility trait also varies substantially within healthy populations (Forster and Lavie, 2015), providing a useful means of indexing variability between participants, which we exploit in Chapter 3.

The attentional-distractor paradigm involves fast, serial target detection (Forster and Lavie, 2008), in the vein of traditional response-competition tasks. Such tasks

require participants to make speeded responses to serially presented letters while distractors are presented in the periphery; distractors are usually response-congruent (distractor Y for target Y) or incongruent (distractor O for target Y) (Eriksen, 1995; Forster and Lavie, 2014). However, it has been suggested that in traditional response-competition paradigms, distractors are closely related to the task at hand, either through response associations or locations (Forster and Lavie, 2008, 2014). Therefore, the attentional-distractor paradigm uses salient but task-irrelevant images (e.g., a cartoon figure). These distractors appear in the minority of trials, and (arguably) provide a more realistic measure of everyday distraction: a reader of this thesis is more likely to be distracted by a recent salient news item— the UK's exit from the European Union, for example—than words in the previous or forthcoming sentence.

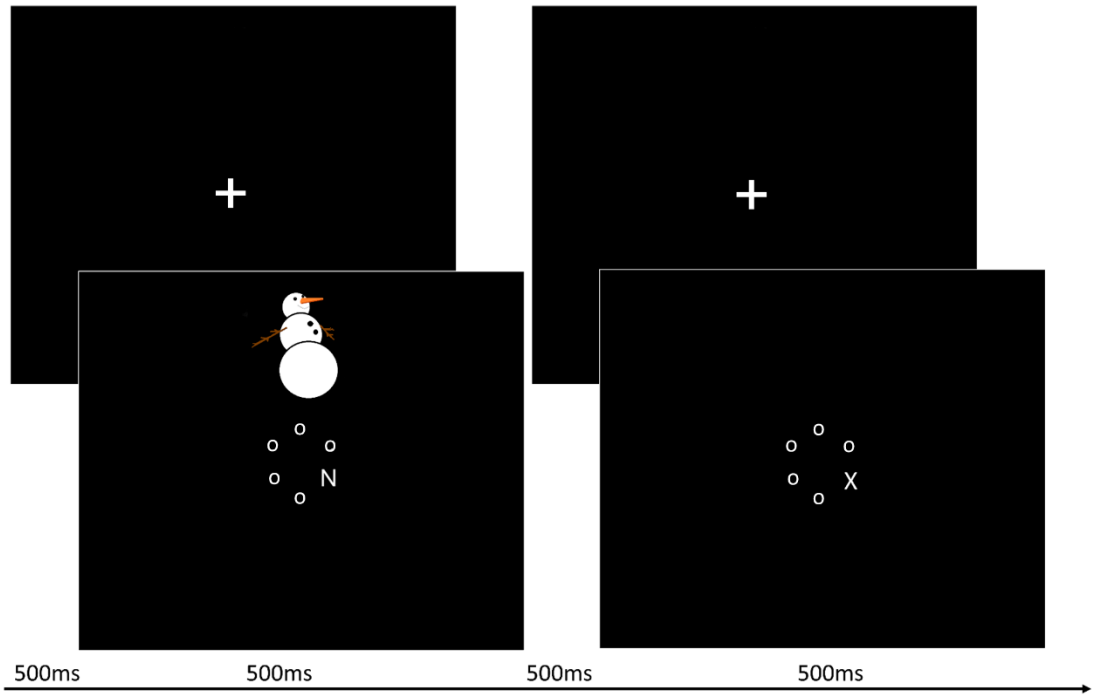

Figure 2.4 Structure of the distraction task. Participants were instructed to press 0 for the target letter X, or 2 for the target letter N, as quickly and accurately as possible. The left trial is an example of an irrelevant distractor trial (10% of trials), and the right trial is an example of a typical trial (90% of trials). Figure reproduced from Nord et al. (2017), *Social Cognitive and Affective Neuroscience.*

2.5 Transcranial direct current stimulation

Throughout this thesis, I employ a neuromodulatory technique, anodal tDCS of the left DLPFC, to probe its effect on behaviour, mood, and neural activation (Chapter 3; Chapters 5 and 6). This technique alters neuronal excitability by delivering a low amplitude of constant direct current using electrodes placed on the scalp (Nitsche and Paulus, 2000).

tDCS is delivered by a battery-driven stimulator, and typically applied via a pair of saline-soaked (35cm^2) electrodes (Nitsche and Paulus, 2000), one anodal (positively charged) electrode, and one cathodal (negatively charged) electrode. Placing one or the other electrode over the primary motor cortex (M1) exerts a very different effect:

the anodal electrode increases M1 excitability, while the cathodal electrode decreases M1 excitability, as measured using transcranial magnetic stimulation (Nitsche and Paulus, 2000). Although studies typically report having used ‘anodal’ or ‘cathodal’ stimulation, this classification is imprecise, as both electrodes are always used. Indeed, the montages of two studies using anodal tDCS of the left DLPFC could be very different, depending on the placement of the cathodal (or ‘reference’) electrode (Tremblay et al., 2014).

Placement of the reference electrode demonstrably changes current distribution, even with identical placement of the “active” electrode (Bikson et al., 2010; Moliadze et al., 2010). This limits to the degree to which a montage could be considered ‘excitatory’ or ‘inhibitory’ (Bikson et al., 2010). For example, only an M1-contralateral forehead montage induces significant excitability changes in M1 (Nitsche and Paulus, 2001), but this setup has the significant drawback of inducing excitability changes under the reference electrode. To avoid this, some have suggested using a reference electrode elsewhere on the body (Moliadze et al., 2010). However, there is an inverse relationship between the magnitude of excitability changes induced by tDCS and the distance between the two electrodes (Moliadze et al., 2010).

I endeavoured to minimize the direct cortical effects of the cathodal electrode in our left anodal DLPFC montage by placing it over the ipsilateral shoulder (superior trapezius), i.e. as close as possible to the head without having any chance of inducing brain excitability changes (this is known as an extraencenphalic cathode) (see Figure 1.3). Other studies have used a supraorbital cathodal electrode placement with DLPFC tDCS (Fregni et al., 2005; Lally et al., 2013; Loo et al., 2012) or a bifrontal montage, with the cathodal electrode on the right DLPFC (Brunoni et

al., 2014b), but arguably it is harder to discount the role of the cathodal electrode in these montages. It is important to note, however, that although the position of our cathodal electrode would not have directly affected any cortex itself, its position still has a substantial effect on the distribution of current under and surrounding the anodal electrode (Bikson et al., 2010). In a computational modelling study of tDCS montages used in depression, this left DLPFC anode – extraencaphalic cathode montage was also suggested to induce current flow in central structures, including the anterior cingulate cortex (Bai et al., 2014). The efficacy of this montage received preliminary empirical support in an open-label depression trial (Martin et al., 2011). I employ this montage (left DLPFC anode – extraencaphalic cathode) in Chapter 3, as well as the RCT presented in Chapters 5 and 6.

Chapter 3. Prefrontal cortex stimulation does not affect emotional bias, but may slow emotion identification

3.1 Abstract

Transcranial direct current stimulation (tDCS) has recently garnered attention as a putative depression treatment. However, the cognitive mechanisms by which it exerts an antidepressant effect are unclear: tDCS may directly alter hot emotional processing biases, or alleviate depression through changes in cold (non-emotional) cognitive function. Here, 75 healthy participants performed a facial emotion identification task during 20 minutes of anodal or sham tDCS over the left dorsolateral prefrontal cortex (DLPFC) in a double-blind, within-subject crossover design. A subset of 31 participants additionally completed a task measuring attentional distraction during stimulation. Compared to sham stimulation, anodal tDCS of the left DLPFC resulted in an increase in response latency across all emotional conditions. We failed to show any emotion-dependent effect of tDCS on behaviour. Thus, we find that anodal tDCS produces a general, rather than an emotion-specific, effect. We also report a preliminary finding in the subset of participants who completed the distractibility task: increased distractibility during active stimulation correlated significantly with the degree to which tDCS slowed emotion identification. Our results provide insight into the possible mechanisms by which DLPFC tDCS may treat symptoms of depression, suggesting that it may not alter emotional biases, but instead may affect 'cold' cognitive processes.

3.2 Introduction

Over the past decade a form of noninvasive brain stimulation, anodal transcranial direct current stimulation (tDCS), has been reported to be effective in treating depression, both alone (Boggio et al., 2008; Fregni et al., 2006a; Loo et al., 2012), and in combination with antidepressant medication (Brunoni et al., 2013). Anodal tDCS delivers a weak electric current that modulates cortical excitability, although the precise mechanisms underlying its effects are largely unknown.

Anodal tDCS has been used to directly target one of the most reliably identified neural correlates of depression, dysfunction of the dorsolateral prefrontal cortex (DLPFC) (Fales et al., 2009; Koenigs and Grafman, 2009). At rest, metabolism in the DLPFC has been found to be reduced in depression (Baxter et al., 1989; Biver et al., 1994; Galynker et al., 1998). By contrast, task-related functional magnetic resonance imaging (fMRI) studies have reported both hyper- and hypoactivation in the DLPFC (Elliott et al., 1997a; Harvey et al., 2005; Siegle et al., 2007a; Wang et al., 2015). Hypoactivity in the DLPFC is interpreted as a weaker ability to harness DLPFC activity during difficult tasks (Elliott et al., 1997a; Siegle et al., 2007a); while hyperactivity is interpreted as cortical inefficiency (Harvey et al., 2005). These inconsistencies may be related to between-study differences in task difficulty, with more difficult tasks— when patients are impaired— finding hypoactivation, and vice versa (Wang et al., 2015). Targeting the DLPFC with tDCS therefore aims to remedy this dysfunctional DLPFC activation (Nord and Roiser, 2015), with possible downstream effects on dysregulation in other circuits driving biased emotional processing (Roiser et al., 2012). However, despite preliminary findings of its

antidepressant efficacy (Shiozawa et al., 2014), there is a dearth of research on the cognitive mechanisms that may drive the beneficial effects of DLPFC tDCS.

3.2.1 Hot and cold cognition in depression

As outlined in Chapter 1, among the neural systems implicated in the neurobiology of depression, two networks are thought to play a particularly important role, and have been targeted in the context of novel treatments for depression. The first system is implicated in emotion and reward processing, often termed hot cognition, and includes limbic structures as well as the ventral prefrontal cortex, in particular the sgACC (Drevets et al., 2008). Disruptions in this system are thought to drive the characteristic depressive bias in hot cognition, away from positive and towards negative information processing (Bradley and Mathews, 1983). The second system is associated particularly with effortful 'cold' (non-emotional) cognitive processing, and includes the dorsal anterior cingulate cortex, the hippocampus, and the DLPFC (Roiser and Sahakian, 2013).

If the mechanism driving any antidepressant effects of DLPFC stimulation were similar to that of traditional pharmacological treatments, there might occur an acute effect of tDCS on hot cognition. Although the therapeutic effect of antidepressant drugs typically takes 4-6 weeks, acute doses have been shown to produce positive emotional biases, in both healthy controls (Harmer et al., 2003b) and depressed patients (Harmer et al., 2009b). According to the cognitive neuropsychological model, these effects elicit downstream changes, through the relearning of internal models of the environment (schemata), ultimately resulting in symptom remission (Harmer et al., 2009a).

Despite the central importance of hot cognitive processing in contemporary theories of depression, this area has been almost entirely neglected in tDCS research, though a small number of exceptions exist. In one study, DLPFC tDCS did not elicit subjective emotional changes, but subtly improved identification of positive emotional expressions in healthy subjects (Nitsche et al., 2012); in another, DLPFC tDCS decreased vigilance to threatening stimuli (Ironside et al., 2015), a result akin to the effect of anxiolytic drugs such as diazepam (Murphy et al., 2008). However, in the latter study, tDCS did not affect any other measures of emotional processing in a comprehensive battery of tasks (Ironside et al., 2015).

Another possibility is that DLPFC tDCS exerts an antidepressant effect through mechanisms altogether distinct from those involved in antidepressant drug treatment. Instead, tDCS might only directly affect cold cognitive processing in depression, but this could potentially catalyse the changes in top-down emotional processing that are thought to drive the remission of symptoms, for example by improving reality checking (Roiser et al., 2012). Disruptions in cold cognition in depression, which are part of standard diagnostic criteria, typically manifest as impairments in attention, cognitive control, and working memory, and have been hypothesised to be caused by dysfunction in regions such as the DLPFC (Harvey et al., 2005). There is evidence that anodal DLPFC tDCS improves working memory (Andrews et al., 2011; Lally et al., 2013) and cognitive control (Vanderhasselt et al., 2013). However, there is also evidence that anodal DLPFC tDCS increases self-reported mind-wandering, as measured using subjective reports of task-unrelated thoughts (e.g., “what shall I eat for lunch today?”; versus a task-related thought such as “what is the correct button to press now?”). This is of particular relevance to depression, as a central symptom of depression, rumination, involves fixation on

negative thoughts. Depressive thinking is associated with mind-wandering (Smallwood et al., 2007), but mind-wandering itself does not appear to decrease mood (Poerio et al., 2013). However, distraction has been shown to alleviate depressed mood, potentially through interruption of rumination (Nolen-Hoeksema and Morrow, 1993). If tDCS does indeed increase mind-wandering (Axelrod et al., 2015; Kajimura and Nomura, 2015), this could provide a second possible mechanism for its antidepressant effects: an increase in distraction from negative thoughts.

Drawing on the consistent reports of emotional processing biases in depression, and the evidence that standard antidepressant drugs normalize these, the main aim of this study was to test whether DLPFC tDCS positively biases emotional processing. We used a well-validated task involving the identification of morphed emotional expressions. We hypothesized that if anodal left DLPFC tDCS exerts antidepressant effects through modulating hot cognition, it should elicit a positive bias in emotional face identification, similar to the acute effects of antidepressant drugs. In a subgroup of participants, we also tested a specific hypothesis that tDCS might increase distractibility, due to its previously-reported effect on mind-wandering (Axelrod et al., 2015). To this end, we employed an experimental paradigm that measures the effect of irrelevant distractors on attentional performance (Forster and Lavie, 2008), which has been shown to correlate with internal distraction from mind-wandering (Forster and Lavie, 2014), allowing us to use this as an index of individual variability in distractibility.

3.3 Methods

3.3.1 Participants and procedure

Seventy-five healthy participants (40 females; mean age 25.6) were recruited via the online University College London Psychology Subject Pool. Exclusion criteria included any history of seizures, and any known neurological or psychiatric disorders, which were assessed by telephone interview prior to the first testing session. All participants gave written informed consent before proceeding with the first day of the experiment, for which they were randomized to either active or sham stimulation, which was delivered while completing the cognitive tasks. Both experimenter and participant were blind to stimulation. Participants attended on a second day, at least 24 hours after the first, on which they received the other stimulation type. Participants were compensated for their time and travel, and the study was approved by the NHS Research Ethics Committee for London Queen Square.

3.3.2 Brain stimulation

As described in Chapter 2, anodal transcranial direct current stimulation at 1 mA was generated by a battery-driven stimulator (neuroConn DC-stimulator, Ilmenau, Germany). Sponge coverings were soaked in saline and applied to a pair of 5 x 7 cm electrodes. The anodal electrode was placed over the left DLPFC using the international 10-20 system of electrode placement (Jasper, 1958). The reference electrode was placed on the ipsilateral shoulder deltoid muscle, to ensure that the effects on the brain originated from the anodal stimulation alone (Priori et al., 2008; Wolkenstein and Plewnia, 2013). Anodal and sham stimulation both used an

identical electrode montage with the anodal electrode located at F3 in the 10-20 system, and lasted 20 minutes, but anodal stimulation involved a 5-second ramp-up of stimulation after which the current was delivered continuously, whereas sham stimulation delivered a current for only 30 seconds. Participants were randomized using pre-determined codes to allocate the order of sham versus active stimulation days, with order counterbalanced across participants. In a subset of participants (N=45), we also assessed side-effects using the tDCS Adverse Events Questionnaire (Brunoni et al., 2011) (in N=30 participants, we only assessed spontaneously-reported side-effects).

3.3.3 Emotional faces task

The Emotion Recognition Task, programmed in E-Prime, is a six-alternative forced-choice paradigm to measure sensitivity to six emotions (happy, sad, fearful, angry, surprised, and disgusted). Each trial begins with a central fixation cross lasting 1500-2500ms and presents a morphed face stimulus for 150ms, followed by a 250ms noise mask, to prevent afterimages (Bamford et al., 2015). Participants are then required to select the emotion best describing the facial stimulus, using the mouse to click on one of the six emotion types displayed on screen (see Figure 3.1). The emotion type options appear for 10,000ms or until the participant responds. Participants completed the task in an average of 6.65 minutes (SD=1.18).

The 350 x 457 pixel face stimuli were created from photographs of 12 young adults photographed under controlled conditions, and merged into composite images depicting each of the six emotions (Bamford et al., 2015). A face depicting a prototypical expression was also constructed, made up of a composite of 6 emotional and one neutral expression (Bamford et al., 2015). This was so the face

would appear genuinely emotionally ambiguous, since recent evidence suggests that emotions are coded with reference to a prototype of this nature (rather than a neutral face) (Skinner and Benton, 2010). A 15-image morph sequence that ran along the continuum from the prototypical face to the full-intensity emotional expression was created for each of the six emotions, with the first image displaying 5% intensity, and the final image displaying 100% intensity. In the task, ninety-six choices were made, sixteen per emotion (half male, half female faces).

One participant experienced inconsistent stimulation on both days due to high electrical impedance (which may have occurred due to thick hair (Horvath et al., 2014)), and a data saving failure occurred for a second participant (but whose distractibility task data were saved). Both these participants were therefore excluded from all emotion identification data leaving N=73 in the final analysis.

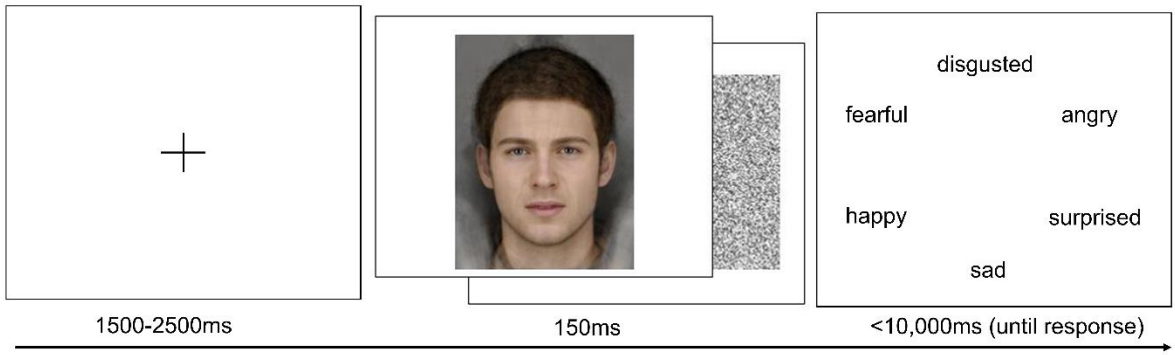

Figure 3.1 Structure of the emotion identification task. Each trial begins with a fixation cross, followed by a very brief presentation (150 ms) of an emotional face which is replaced by a mask. Participants responded using the mouse to identify the emotion presented.

3.3.4 Distractibility task

In a subset of the participants (N=31) we administered an attentional distraction task in addition to the emotional faces task, which was also programmed in E-Prime (Forster and Lavie, 2008). For these participants the distractibility task was always administered first during the stimulation session. All stimuli were presented on a

laptop screen at a viewing distance of 60cm. Each trial begins with a centrally-presented fixation point shown for 500ms, followed by the stimulus, which consists of a 1.6º radius circle of grey letters (‘o’) presented on a black background. Participants are instructed to search the stimulus display for a target letter (either X or N, presented for 500ms), for which they make a rapid keyboard response (pressing 0 or 2 for X or N, respectively). Participants complete three slow (1000ms) example trials, and 12 fast (500ms) practice trials, before beginning the full version (480 trials). The task last an average of 8.19 minutes (SD=30.6 seconds). An irrelevant distractor (a cartoon character) is presented in the periphery of the screen, outside the letter circle, on 10% of trials (distractor condition). Participants are directed to respond as quickly and accurately as possible, and to focus only on the letter circle, ignoring any stimulus outside the circle (see Figure 2.4). Feedback for errors is provided by a brief tone.

The main outcome measure on this task contrasts responses on trials where no distractor was presented with those on which the irrelevant distractor was presented (Forster and Lavie, 2008). In other words, it provides a measure of how distractible a participant is by measuring the degree to which distracting stimuli affect errors and reaction times. This enabled us to test whether (1) anodal tDCS of the DLPFC increased distraction on the task, and (2) whether the effect of tDCS on distraction correlated with any effects of tDCS on emotion identification.

At eight intervals throughout the task, participants were additionally presented with thought probes asking “What were you thinking about just now?”, and instructed to answer whether or not they had experienced task-unrelated thoughts (TUTs) in the trials leading up to the question.

In the thought probes, participants were instructed to report the thought that had been passing through their mind in the moment immediately before the probe appeared. Participants were instructed to press A if they were thinking about the task that they were performing (they were given examples of “where is the target letter?” and “oops I’ve pressed the wrong button”), and to press Z if they were thinking about something unrelated to the task at hand. Thus, our measure of TUTs reflects only the proportion of probes to which participants reported task-unrelated versus task-related thoughts.

3.3.5 Statistical analysis

Statistical analyses were performed in SPSS 22.0 (IBM Comp, Armonk, NY). Repeated-measured analyses of variance (ANOVAs) were constructed to examine how sham or active tDCS affected accuracy and reaction times for each of the six emotion types (for the emotion task) or the two distraction conditions (for the distraction task). We initially included order as a between-subjects factor in all models, and removed it if there was no significant effect of order or any interactions.

Finally, in the subgroup of participants who completed both tasks, we calculated a measure of the degree to which distractibility (measured by reaction time) was altered by tDCS as:

[distractor condition (active tDCS) – no distractor condition (active tDCS)] –

[distractor condition (sham tDCS) – no distractor condition (sham tDCS)]

We correlated this tDCS-induced distractibility measure with tDCS-induced changes in reaction times on the emotion identification task, using Pearson's correlation coefficient.

3.3.6 Power analysis

A previous report of tDCS on attentional vigilance reported an effect size of d=0.87 (Ironside et al., 2015). Therefore, for a within-subjects design, 20 subjects were required to achieve 95% power (2-tailed test). However, we powered our study to detect a smaller effect size (d=0.5), since initial effect size estimates are frequently inflated (Button et al., 2013). Therefore, in the emotion task, with 73 participants, we had 99% power to detect an effect size of 0.5 at $\alpha = 0.05$ (2-tailed); in the distractibility task, with 31 subjects, we had 77% power to detect this moderate effect size (and 99% power to detect the previous effect size of 0.87). Finally, for the between-task correlation, with 31 subjects, we had 86% power to detect a true association of r=0.5 at α=0.05 (2-tailed).

3.4 Results

3.4.1 Side effects

Common side-effects of tDCS were recorded for both active and sham tDCS sessions, including itching, burning, and tingling. These effects were no more common under active tDCS than sham stimulation (for a full list of reported side-effects, see Table 3.1).

% Reporting	Active tDCS	Sham tDCS
Headache	7%	7%
Neck pain	4%	5%
Scalp pain	9%	9%
Tingling	37%	35%
Itching	37%	31%
Burning sensation	17%	17%
Skin redness	9%	5%
Sleepiness	24%	28%
Trouble concentrating	17%	27%
Acute mood change	8%	9%
Others	1%	4%

Table 3.1 Side effects reported by participants. "Others" included abnormal metallic taste (reported during sham), and numbness in the contralateral side of the face (reported during active).

3.4.2 Emotion identification task

For the reaction time analysis, there was a significant stimulation-by-order interaction ($F(1,71)=26.39$, $p<0.001$), representing a practice effect by which participants responded faster on the second testing session regardless of stimulation. Therefore order (and where relevant the stimulation-by-order interaction) was retained in the reaction time model.

For the accuracy analysis, order of stimulation was removed since no significant interaction between order and stimulation condition was found.

3.4.2.1 Effect of tDCS and emotion on reaction times

The analyses below were performed using reaction time data for correct responses only, but the results were similar when including all responses (data not shown). Participants responded significantly more slowly under tDCS ($F(1,71)=6.02$,

p=0.017). Reaction times were also significantly affected by emotional valence (F(5,355)=7.4, p<0.001), with happy, sad, and surprise eliciting shorter reaction times than fear, anger, and disgust (Figure 3.2A). Paired contrasts revealed that reaction times to angry faces were significantly longer than to happy (t(72)=3.98, p<0.001), sad (t(72)=3.29, p=0.002), and surprised faces (t(72)=5.80, p<0.001), but not fearful (t(72)=1.29, p=0.201) or disgusted (t(72)=1.63, p=0.108); while disgusted faces were identified significantly more slowly than happy (t(72)=2.82, p=0.006) and surprised faces (t(72)=3.97, p<0.001) (but not fearful (t(72)=-0.18, p=0.862) or sad (t(72)=1.35, p=0.182)). Additionally, fearful faces were identified significantly more slowly than happy (t(72)=2.40, p<0.019) and surprised faces (t(72)=3.94, p<0.001) (but not sad (t(72)=1.40, p=0.166)), and sad faces were identified significantly more slowly than surprised faces (t(72)=2.68, p=0.009). There was no interaction between stimulation and emotion type on reaction times (F(5,355)=0.26, p=0.93).

3.4.2.2 Effect of tDCS and emotion on accuracy

We did not find a significant main effect of stimulation on accuracy (F(1,72)=1.62, p=0.21). However, accuracy depended significantly on emotion (F(5,360)=31.95, p<0.001) (Figure 3.2B). Accuracy was higher for identifying happy, sad, and surprised faces, and lower for identifying fearful, angry, and disgusted faces. Paired contrasts revealed that fear was identified significantly less accurately than all other emotions: anger (t(72)=4.48, p<0.001), disgust (t(72)=6.70, p<0.001), happy (t(72)=8.68, p<0.001), sad (t(72)=8.30, p<0.001), and surprise (t(72)=7.59, p<0.001). Anger was also identified significantly less accurately than: disgust (t(72)=3.87, p<0.001), sad (t(72)=5.76, p<0.001), happy (t(72)=6.58, p<0.001) and surprise (t(72)=5.84, p<0.001). Disgust was identified significantly less accurately than happy

($t(72)=2.67$, $p=0.009$), but not sad ($t(72)=1.07$, $p=0.290$) or surprise ($t(72)=0.91$, $p=0.367$); while happy was identified significantly more accurately than surprise ($t(72)=2.1$, $p=0.039$), but not sad ($t(72)=1.86$, $p=0.068$). We did not find a significant stimulation-by-emotion interaction ($F(1,72)=1.33$, $p=0.25$).

The slowing effect of tDCS on emotional face identification did not correlate with either the severity or frequency of side effects. We calculated the difference in severity and number of side effects between active and sham conditions, and tested its association with the slowing effet of tDCS on emotional face identification (severity: Pearson's $r(45)=0.051$, $p=0.737$; frequency: $r(45) =0.205$, $p=0.178$). These correlations were only performed in the subset of participants who completed a systematic side-effects questionnaire (Brunoni et al., 2011); 30 participants were not included in this analysis because we only recorded spontaneous reports of side-effects in that subset.

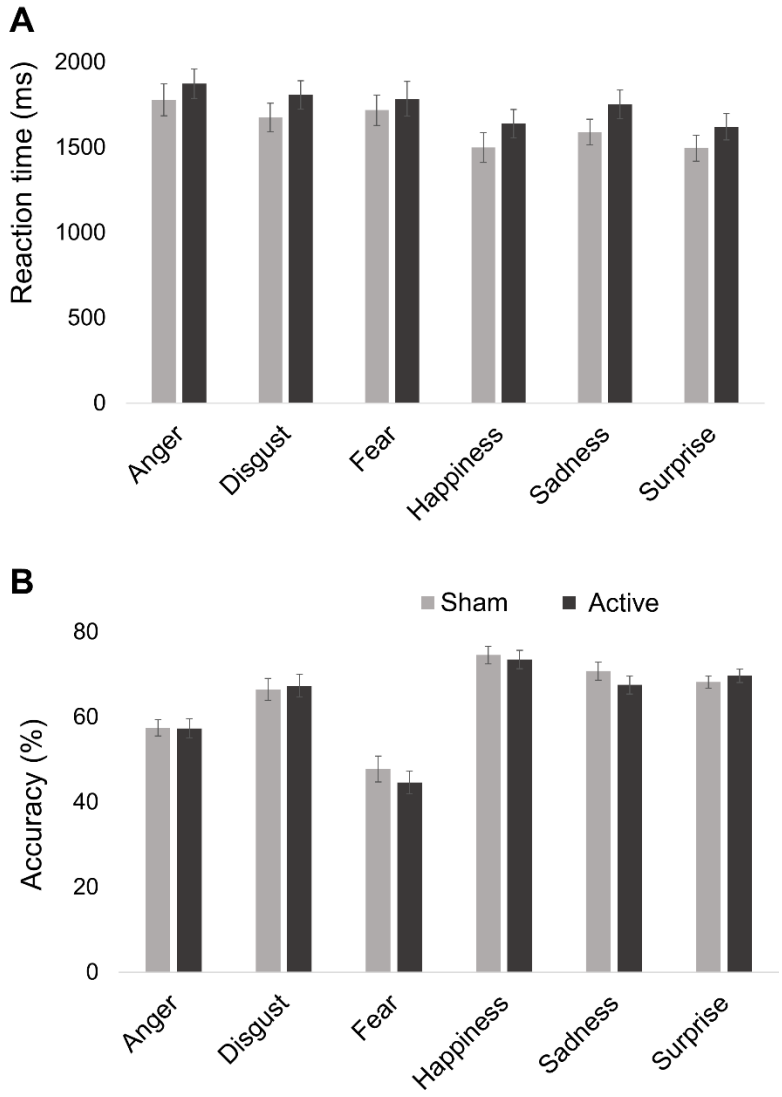

Figure 3.2 Behaviour on the emotion task. 3.2A: Mean reaction times by emotion category. Sham stimulation (light grey bars), was associated with shorter reaction times across all emotions on average than active (anodal) tDCS stimulation (dark grey bars) (p=0.017). 3.2B: Mean percent accuracy by emotion category. There was no significant difference in accuracy between sham stimulation and anodal tDCS stimulation. Error bars represent standard errors of the mean.

3.4.3 Distraction task

There was a significant stimulation-by-order interaction for both reaction time (F(1,29)=12.33, p=0.001) and accuracy (F(1,29)=10.04, p=0.004). These results represent practice effects by which participants performed faster and more accurately on the second testing session, regardless of stimulation. Therefore order (and where relevant the stimulation-by-order interaction) was retained in both models.

TUT responses had a highly skewed distribution, so we employed a non-parametric Wilcoxon Signed-Ranks Test. This showed that task-unrelated thoughts increased under active stimulation relative to sham, though this effect narrowly missed statistical significance (Z=1.84, p=0.067).

3.4.3.1 Effect of tDCS and distraction on reaction times

As expected, distraction significantly slowed responses (F(1,29)=65.6, p<0.001; Figure 3.3A). There was no main effect of stimulation on reaction times (F(1,29)=0.059, p=0.81), and no interaction between stimulation and distraction condition (F(1,29)=0.35, p=0.56). We additionally examined whether subjective ratings of mind-wandering (TUTs) were associated with slower reaction times in the distractor condition, but could not confirm this hypothesis (correlations employed Spearman's rank-order correlation, due to the skewed distribution of TUTs. For active stimulation: r_s(31)=0.037, p=0.903; for sham stimulation: r_s(31)=-0.023, p=0.842).

3.4.3.2 Effect of tDCS and distraction on accuracy

tDCS significantly improved overall accuracy compared with sham stimulation (F(1,29)=7.30, p=0.011, Figure 3.3B), and distraction significantly impaired accuracy (F(1,29)=5.46, p=0.027). No significant interaction was found between stimulation and distraction condition (F(1,29)=0.92, p=0.345, Figure 3.3B).

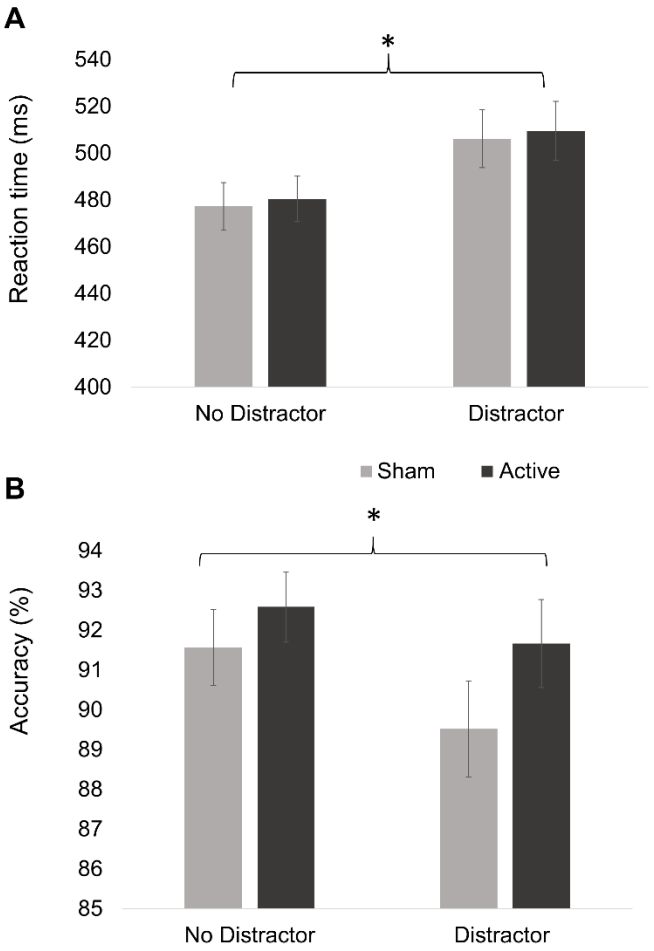

Figure 3.3 Behaviour on the distraction task. 3.3A: The effects of tDCS and distraction condition on reaction times. As expected, the condition with distractors elicited significantly slower responses (*p<0.001), but there was no significant effect of tDCS on reaction times. 3.3B: The effects of tDCS and distraction condition on accuracy. The presence of distractors decreased accuracy, and accuracy was higher in the active (anodal tDCS: dark grey bars) condition than in the sham (light grey bars) condition (*p=0.011), but the interaction was non-significant. Error bars represent standard errors of the mean.

3.4.3.3 Relationship between distractibility and emotion identification latency

We calculated a variable reflecting the effect of anodal tDCS on distractibility as assessed by reaction times (RTs). This was essentially the interaction effect between distractibility and tDCS: distractibility (distractor – no distractor condition RT) under active tDCS minus distractibility (distractor – no distractor condition RT) under sham tDCS. This enabled us to test whether the effect of tDCS on lengthening reaction times on the emotional face identification task was driven by its effect on distractibility. We found that the extent to which tDCS slowed responses to

emotional faces correlated positively with the increase in distractibility under tDCS (r=0.37, p=0.043; Figure 3.4).

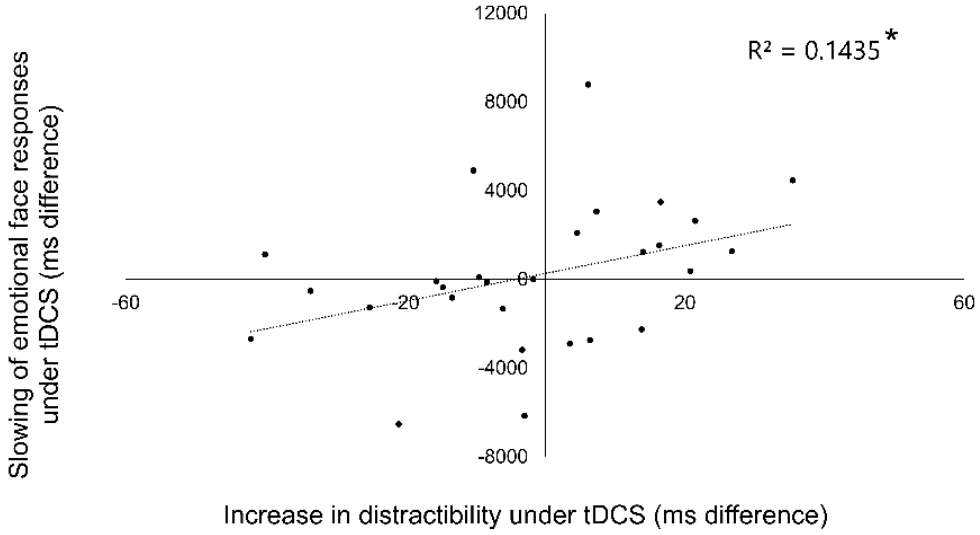

Figure 3.4 Relationship between tDCS effects on latency and distractibility. There was a positive relationship between increased distractibility (the increase in reaction time in the distractor condition, relative to the no-distractor condition, on the distractibility task) under tDCS, and increased reaction times on the emotional faces task under tDCS. *p=0.043.

3.5 Discussion

The main aim of this experiment was to test whether DLPFC tDCS affected hot and cold cognitive processing. We first investigated whether anodal DLPFC tDCS had acute effects on emotion identification. We hypothesized that tDCS might have an effect similar to antidepressant drugs, improving or speeding responses to positively-valenced faces, and/or impairing or slowing responses to negatively-valenced faces. We did not find this predicted interaction in either reaction times or accuracy scores. Instead, we identified a significant slowing of responses by tDCS on average across all emotional conditions. This suggests that tDCS did not have a valence-specific effect on emotional face identification. Additionally, we did not identify a corresponding improvement in accuracy (i.e., a speed/accuracy trade-off) as a result of tDCS; in other words, participants became slower, but not better, at categorizing emotional faces. This pattern of results indicates that tDCS may have an effect on emotional deliberation. One interpretation is that tDCS may make participants more uncertain about what emotional category a face belongs to.

In a subset of our participants, we tested a specific hypothesis that anodal DLPFC tDCS has an effect on distraction, using a task with the ability to index distractibility during active and sham tDCS sessions. We found that those participants whose distractibility increased most under tDCS were also those who showed an increased latency in the emotion identification task under tDCS. This task, which has previously been shown to correlate with internal distraction from mind-wandering (Forster and Lavie, 2014), also enabled us to test the basic effect of tDCS on distractibility with somewhat surprising results. We found that overall accuracy increased significantly under anodal tDCS, but that distractibility itself was not affected. Significantly

improved accuracy under anodal tDCS is consistent with the finding that anodal tDCS over the frontal cortex increases alertness (Coffman et al., 2014), perhaps by enhancing vigilance (Nelson et al., 2014). We also found a trend towards increased mind-wandering during anodal tDCS, which has been previously reported (Axelrod et al., 2015). However, it should be noted that the behavioural effects of tDCS vary substantially between studies (Tremblay et al., 2014), causing some authors to cast doubt on the effects of tDCS on cognition altogether (Horvath et al., 2015).

3.5.1 Relationship to mind-wandering in depression

Our findings suggest that tDCS does not instantiate a positive emotional bias in emotion identification, unlike antidepressant medication. Instead, our findings could implicate cold cognitive processes in the acute effects of tDCS. The possibility that attentional mechanisms, such as distractibility, might mediate the effects of tDCS has particular implications for treating attentional symptoms of depression. Two previous studies reported increased mind-wandering (task-unrelated thoughts) under anodal tDCS of the DLPFC (Axelrod et al., 2015) and left PFC (Kajimura and Nomura, 2015), although in our study this effect narrowly missed statistical significance. However, the relationship between the recently-described effect of tDCS on self-reported mind-wandering (Axelrod et al., 2015) and its putative antidepressant effects has so far been unexplored. Some studies have supported the notion that negative mood increases task-unrelated thoughts (Smallwood et al., 2009), enhancing focus on task-irrelevant personal concerns; indeed, mind-wandering has even been suggested as a marker for ruminative thinking (Smallwood et al., 2007). Yet there seems to be an inherent contradiction in the notion that mind-wandering is increased in depression (Smallwood et al., 2007), that tDCS increases

mind-wandering (Axelrod et al., 2015), and that tDCS is an effective treatment for depression (Shiozawa et al., 2014).

One possible resolution to this apparent contradiction lies in whether mind-wandering is truly a unidimensional phenomenon. While mind-wandering is typically measured in a binary way (e.g., “Have you had any task-unrelated thoughts?”), it is much more likely that factors such as the valence of mind-wandering or when the mind wanders affect the subjective experience. For example, if mind-wandering occurs in a distressing environment, or while trapped in a train of negative thought, then it may be adaptive and useful. This idea is supported by a finding that mind-wandering itself does not precede the onset of depressive thoughts (though the inverse is true): only affectively negative mind-wandering has mood dampening effects (Poerio et al., 2013). Since we did not test depressed patients, our study cannot address whether the tendency of tDCS to increase mind-wandering is related to its putative antidepressant effects. It will be important to test this hypothesis in future studies. Indeed, the well-described symptom of rumination in depression could be viewed as the inverse of mind-wandering, reflecting a single circular, repetitive train of negative thoughts. This is substantiated by evidence that a brief distraction induction reduces over-general autobiographical memory (Watkins et al., 2000), a phenomenon in depression that is associated with poor outcome (Kuyken and Brewin, 1995). In the same study, rumination induction maintained over-general memory (Watkins et al., 2000). In other words, rumination and mind-wandering are not only separable, but they may even function in opposition to one another in some cases. The previous hypothesis of increased mind-wandering in depression (Smallwood et al., 2007, 2009) does not take these components of the phenomenon into account. This hypothesis could be tested directly by measuring the effect of

tDCS on attentional set shifting; the explanation proposed above would predict that tDCS would improve set shifting, a marker for cognitive flexibility, on which depressed patients are known to perform poorly (Rock et al., 2014).

3.5.2 Limitations

Two important caveats to our results bear mentioning: first, the reaction time measurement in this task involved a fairly complex motor action (moving the mouse to click), and may differ substantially from more typical (highly speeded) reaction time measurements. This limits our ability to draw parallels with other reaction time tasks, though would not affect the differences we report between sham and anodal stimulation. Additionally, although we employ a typical tDCS montage used in depression (anodal left DLPFC stimulation), we specifically recruited healthy controls. It would be essential to show a similar pattern findings in a depressed sample to draw clear conclusions about the role of cold cognition and distractibility in tDCS for depression. We also note that, while our finding of a lack of emotional bias induced by tDCS was robust, the observed relationship between slowing of emotional identification and distractibility was weak and should be interpreted with caution. In particular, we cannot rule out the possibility that the latter correlation might reflect a generic disruptive effect of tDCS on the demanding aspects of cognitive and emotional tasks, which requires testing in future studies.

3.5.3 Conclusion

Few previous studies have investigated the effects of tDCS on hot and cold cognition, though both are thought to contribute to the pathogenesis of depression (American Psychiatric Association, 2003), and are associated with response to

antidepressant medication (Potter et al., 2004). We show that a tDCS montage commonly used in depression trials does not affect low-level hot cognition, but may slow emotion identification by increasing distractibility. This finding suggests that the antidepressant effects of tDCS may involve relatively distinct cognitive mechanisms from antidepressant medication. We further investigate the cognitive and neural mechanisms associated with DLPFC tDCS in a depressed population in Chapters 5 and 6, after characterising the nature of DLPFC dysfunction in risk for depression in Chapter 4.

Chapter 4. Prefrontal and subcortical responsivity in patients with depression, unaffected first-degree relatives, and healthy controls

4.1 Abstract

The neural features governing risk and resilience to depression are largely unknown. The cognitive neuropsychological model of depression posits that biased emotional (hot) processing confers risk for depression, while preserved non-emotional (cold) cognition might help mitigate this risk. However, few studies have compared samples at risk of depression and those currently experiencing a major depressive episode on neural responses during hot and cold cognition, which could test this theory. We recruited 99 participants: 39 unmedicated currently-depressed patients, 30 unaffected (and unrelated) first-degree relatives of depressed individuals, and 30 age- and sex-matched healthy controls. We assessed two potential neural mechanisms that have previously been associated with depression: dorsolateral prefrontal cortex (DLPFC) responsivity during working memory, using the n-back task; and amygdala and subgenual anterior cingulate cortex responsivity during emotion processing, using an incidental emotion processing task. Our findings indicate that unaffected first-degree relatives of depressed patients show bilateral DLPFC activation that is similar to healthy controls, while depressed patients show attenuated activation during working memory. These results are consistent with preserved cold cognitive processing in unaffected relatives of depressed individuals, consistent with the notion that preserved cold cognitive function may confer resilience to depression. However, we did not observe a complementary pattern on the emotion processing task: here, neither unaffected relatives nor currently

depressed patients showed aberrant sgACC or amygdala responsivity compared to healthy controls. These results have important implications for understanding the neural mechanisms of risk and resilience in depression, which we interpret in the context of the cognitive neuropsychological model of depression. Specifically, these results are at least partially consistent with the proposal that preserved “cold” dorsal prefrontal cortical function might furnish resistance to developing depression. However, we did not find evidence that risk in unaffected relatives might be conferred through disrupted processing of “hot” emotional stimuli.

4.2 Introduction

Family history plays a large role in the development and maintenance of major depressive disorder (MDD). First-degree relatives of patients with MDD have a two-to-fourfold increased risk for MDD than those without a family history of depression (Weissman et al., 1993). Depressed patients with a family history of MDD show a lower age of onset, and are more likely to have recurrent depression (Hollon et al., 2006a). Indeed, a recent epidemiological study found that this risk is compounded in individuals with two previous generations affected by MDD, who show an even higher risk (Weissman et al., 2016).

MDD is notably less heritable than other mental illnesses. The heritability of depression is estimated at approximately 40% (Kendler et al., 2001; McGuffin et al., 1991, 1996; Sullivan et al., 2000; Torgersen, 1986), in contrast to psychotic disorders, estimated at over 80% (Cardno et al., 1999). Therefore, an at-risk sample (with a positive family history, but no personal history of mood disorder) would also be expected to show protective or resilience factors in relation to the development of MDD.

Over the past decade, fMRI studies have begun to shed light on the neural basis of risk and resilience factors for depression, with most focusing on emotional (hot) cognitive processing, and neural dysfunction in relevant limbic regions. For the most part, these studies report differences in activation between at-risk relatives and healthy controls that mirror neural abnormalities in MDD. In some studies, both MDD patients and at-risk samples showed heightened activation in subcortical regions (Monk et al., 2008), though this was not found in all studies (Mannie et al., 2011).

First-degree relatives of patients with bipolar depression showed exaggerated amygdalar responses to emotional faces compared to healthy controls, comparable to bipolar patients themselves (Olsavsky et al., 2012; Surguladze et al., 2010). Similarly, participants who scored highly on neuroticism (which is associated with a heightened risk of MDD) showed greater activation in the right fusiform gyrus and middle temporal gyrus to facial expressions of increasing fear intensity (Chan et al., 2009). Neural responses to reward processing in at-risk individuals also follow a pattern akin to that observed in MDD patients, with diminished responses reported in the orbitofrontal cortex (OFC) to rewards (McCabe et al., 2012), and greater OFC activation to aversive outcomes (McCabe et al., 2012) and omitted rewards (Macoveanu et al., 2014); the latter was attenuated following administration of the antidepressant escitalopram (Macoveanu et al., 2014). Thus, at least in the domain of hot cognition, at-risk samples frequently show neural commonalities with MDD patients.

Far fewer studies have examined the neural basis of cold (non-emotional) cognition in samples at risk of MDD. During the n-back verbal working memory task, at-risk participants showed greater activation in the lateral occipital cortex, superior temporal cortex, and superior parietal cortex, compared to healthy controls (Mannie et al., 2010). This was interpreted as indicating that successful working memory requires proportionately greater activation in these cortical regions in at-risk individuals. Although no depressed patients were included in this sample, there is separate evidence that MDD patients also show aberrant activation in working memory-related regions, particularly the dorsolateral prefrontal cortex (DLPFC), with some studies reporting greater DLPFC activation than matched healthy controls (Harvey et al., 2005). A recent meta-analysis of 11 studies reported greater lateral

prefrontal cortex activation during n-back performance, which may reflect compensatory neural processes (Wang et al., 2015). However, somewhat paradoxically, a number of other studies have found DLPFC hypoactivation during working memory in MDD (Baxter et al., 1989; Bench et al., 1993; Siegle et al., 2007a). Additionally, normalizing DLPFC activity has been suggested as critical in both psychological and pharmacological therapy for depression (Brody et al., 2001b; Goldapple et al., 2004).

Few studies have investigated both hot and cold cognition-related neural activation in depression (Siegle et al., 2002, 2007a), and none (to our knowledge) also include at-risk groups. The cognitive neuropsychological model of depression predicts that top-down prefrontal mechanisms (corresponding to cold cognitive processing) may mediate resilience by dampening down bottom-up emotional (hot cognitive) biases which confer risk in depression (Roiser et al., 2012). However, because the neural correlates of emotional and non-emotional cognition are typically investigated in separate studies, the relationship between prefrontal and limbic regions in depression and their role in risk and resilience has not yet been established.

Some studies have suggested distinct roles for hot and cold cognitive mechanisms in the risk for depression. In one PET study, induced sadness evoked greater anterior cingulate and anterior insula blood flow in both at-risk siblings and medicated bipolar patients, compared to healthy controls. By contrast, at-risk individuals showed greater medial frontal cortex blood flow, while patients showed less, compared to controls (Krüger et al., 2006). This difference between the patient and at-risk groups was interpreted as a compensatory response, potentially conferring resilience. Another study using fMRI suggested that intact prefrontal function might constrain

aberrant limbic activity: exaggerated limbic responses to fearful faces were only apparent when attention was unconstrained (i.e., passive viewing): the at-risk sample showed no differences when attention was constrained (Monk et al., 2008). Constraining attention was interpreted to have harnessed prefrontal cortex mechanisms in the high-risk sample, tempering the otherwise-abnormal limbic responses.

Hence, it is possible that family risk for depression differentially affects frontal activation during cold cognitive processing and subcortical emotion circuitry during hot cognitive processing. This would align with the predictions of the cognitive neuropsychological model of depression, which hypothesizes that disrupted emotion processing might mediate risk of developing depression, while intact cold cognitive mechanisms might confer a protective factor that promotes resilience (Roiser et al., 2012). To our knowledge, this hypothesis has never been tested directly. Therefore we probed the function of both executive and emotion processing circuits in a sample of depressed patients, unaffected first-degree relatives of depressed patients, and healthy controls without a family history of depression. To this end, we employed two cognitive tasks, one a measure of hot cognition (incidental emotional faces), and the other cold cognition (working memory). We then examined differences between the groups in *a priori* hypothesized regions: the DLPFC (for the working memory task) and the amygdalae and subgenual anterior cingulate cortex (for the emotional faces task).

4.3. Methods

4.3.1 Participants

Ninety-nine participants (46 males) fluent in English were recruited through the UCL Institute of Cognitive Neuroscience subject database (in the case of healthy controls (N=30) and first-degree relatives (N=30)) and Camden and Islington NHS Foundation Trust (in the case of depressed patients (N=39)).

All participants were screened for current or past psychiatric disorders using the Mini International Neuropsychiatric Interview (MINI), version 5.0.0 (Sheehan et al., 1998). Exclusion criteria for the healthy control group and the at-risk sample included history of any neurological or mental health conditions, including: unipolar or bipolar depression, mania or hypomania, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, agoraphobia, post-traumatic stress disorder, psychosis, substance abuse or dependence, and bulimia or anorexia nervosa. Additionally, in all three groups, illegal substance use was prohibited in the six weeks preceding the MRI scan, and standard MRI safety restrictions applied. The healthy control and first-degree relative groups were also administered the Family Interview for Genetic Studies (FIGS), which screened for history of depression in any first-degree relatives (an inclusion criterion for the first-degree relative group, and an exclusion criterion for the healthy control group).

All depressed patients met DSM-IV criteria for a current major depressive episode. Exclusion criteria for the depressed patients were: any history of mania (including hypomanic episodes), substance abuse or dependence (save for a remote history of abuse/dependence restricted to a prior major depressive episode), and use of any

psychotropic medication in the previous six weeks. Family history of depression was assessed as part of the clinical interview in depressed patients (with the question “do you have a parent, sibling, or child who has ever been diagnosed or treated for depression?”).

Participants were compensated £10/hour. The study was approved by the London Queen Square NHS Research Ethics Committee (ID: 13/LO/1028).

4.3.2 Clinical and cognitive measures

We collected the following measures from all participants: mood, measured using the BDI and the HAM-D; anxiety, measured using the BAI; and anhedonia, measured using the SHAPS. In participants who were native English speakers (N=73), we also measured FSIQ, which we calculated using the WTAR (Wechsler, 2001). In depressed patients we also recorded age of onset, number of depressed episodes, treatment history (medication and behavioural therapy), history of hospitalizations, and history of suicide attempts.

4.3.3 Experimental procedure

Subjects were tested on two separate days. The first day involved initial screening for psychiatric conditions and MRI contraindications and a practice session of the n-back task, to ensure participants understood all task instructions. On the second testing day, participants completed the MRI scan, which involved the acquisition of one anatomical scan, and two functional scans (with echo planar imaging, EPI) and fieldmaps (one for each task). Subjects used an MRI-compatible button box to make responses during the tasks. See Table 4.1 for task characteristics.

4.3.2.1 n-back working memory task (Lally et al., 2013)

The n-back consisted of a continuous sequence of letters (four consonants, chosen to be visually distinct from one another), which were centrally presented for 1000 ms, interleaved with fixation crosses presented for 500 ms. Participants were instructed to press a button with the index finger of their right hand whenever the on-screen letter matched the letter 3-back (in the 3-back blocks) or when the on-screen letter matched the letter 1-back (in the 1-back blocks). The task consisted of 27 blocks in total: 9 blocks of 12 letters each for the 3-back and 1-back, and 9 rest blocks. The task was coded in MATALB (release 2015a for Windows, Mathworks, Natick, MA, USA) using the Cogent Toolbox (http://www.vislab.ucl.ac.uk/cogent_2000.php).

Participants were trained on the n-back task on the screening day by briefly exposing them to a 1-back, 2-back, and finally 3-back version. After successfully performing all three levels, participants then completed a shortened (5 minute) version of the scanner task. We calculated accuracy (d') for each participant's n-back data collected in the scanner.

4.3.2.2 Incidental emotion processing task (O'Nions et al., 2011)

Participants viewed faces displaying happy, fearful, and neutral emotions, and were instructed to classify the gender of each face. Participants were instructed to press their index finger to respond to female faces, and their middle finger to respond to male faces. Each participant was presented with a random order of male and female faces, with an equal proportion of male and female faces. The task was made up of twelve blocks, each consisting of a single emotion, with eight stimuli per block; each emotional condition block occurred four times in each run. Faces were displayed for

2 seconds, with each block lasting 16 seconds. Between each block, a central fixation cross was displayed for 16 seconds. All face stimuli were sourced from the NimStim Face Stimulus Set (http://www.macbrain.org/resources.htm) (Tottenham et al., 2009).

	n-back task	Incidental emotion processing
Task duration (min:sec per run)	8:56	6:24
Task design	Blocked	Blocked
Regressors of interest	3-back; 1-back	Happy; fearful; neutral
Regressors of no interest	6 movement parameters	6 movement parameters + errors
Contrasts of interest	3-back > 1 back	happy > neutral fearful > neutral faces > fixation

Table 4.1 Characteristics of each task.

4.3.3 MRI acquisition and analysis

For each task, we acquired gradient-echo T2*-weighted images using a Siemens Avanto 1.5 Tesla MRI scanner (32-channel head coil), with 36 slices per volume. For the emotion processing task, slice thickness was 2 mm; slice thickness was 2.5 mm in the n-back task to allow fuller brain coverage including the dorsal prefrontal cortex. All other parameters were the same between the tasks: echo time was 50 ms, repetition time per slice was 87 msec, and in-plane resolution was 2 x 2 mm. We

acquired one fieldmap per subject per day with the identical volume and parameters of each EPI scan, and one five-minute magnetization-prepared rapid gradient-echo T1-weighted 1 mm isotropic anatomical scan for each subject.

EPI data were analysed using Statistical Parametric Mapping (SPM12; Wellcome Trust Centre for Neuroimaging, London, www.fil.ion.uck.ac.uk/spm) in Matlab R2015a. After removing the first six volumes from each time series to allow for T1 equilibration, the remaining volumes were realigned to the seventh volume, coregistered to each subject's anatomical scan, normalized into standardized space (Montreal Neurological Institute template), and smoothed using an 8 mm full width at half maximum Gaussian kernel. Following the realignment stage, all image sequences were checked for movements greater than 1.5 mm or rotations greater than 1 degree in any direction – corrupted images were removed and replaced using interpolation. Following normalization, anatomical images were manually checked for artefacts related to overfitting.

One participant (a first-degree relative) was excluded from all subsequent n-back task analysis due to a large amount of head movement, which could not be corrected (total analysed in n-back task: N=98); however, this participant was included in all analyses of the emotion processing task (N=99).

Regressors of interest (see Table 4.1) were convolved with a synthetic hemodynamic response function time-locked to the onset of the corresponding event (for the faces task, each 16-second emotion block; for the n-back task, each 18-second 3- or 1-back block). We included six movement regressors of no interest in all subjects, and an error regressor of no interest only in subjects who made gender

discrimination errors on the emotion processing task. In the emotion processing task, fixation periods constituted an implicit baseline. Using the general linear model, parameter estimate images were estimated for each regressor, and combined to create contrasts for each task (see Table 4.1).

Second-level analyses were conducted using the standard summary statistics approach to random effects analysis. To identify the DLPFC, we used a 10 mm-radius sphere centred on coordinates for the left DLPFC from a meta-analysis of 13 studies using the n-back task in depressed patients and healthy controls (coordinates: -44, 20, 30) (Wang et al., 2015). We also used the corresponding coordinate on the right (44, 20, 30: the right DLPFC was not significant in this meta-analysis). We used anatomical ROIs to identify the amygdalae (WFU Pickatlas, version 3.0.5) and sgACC (Nord et al., 2017a). For any small volume-corrected results, we also corrected for the number of ROIs applied.

We first report whole-brain activation across all participants for the 3-back>1-back contrast and its inverse in the n-back task, and for the fearful>neutral, happy>neutral, and faces>fixation contrasts (and their inverses) for the emotion processing task. For these analyses of the main task effects we applied a cluster-forming threshold of $p<0.05$ (family-wise error (FWE)-corrected) and report p-values at the voxel- and cluster-corrected levels. We also report small volume-corrected (SVC) activation in our ROIs (for the n-back task, right and left DLPFC; for the emotion processing task, the amygdalae and sgACC).

We then tested for group effects in two ways. First, we extracted the average parameter estimate across all voxels in each ROI for each subject. For the emotion

processing task, we extracted the average parameter estimate for each subject for our two contrasts of interest (happy>neutral and fearful>neutral faces) for the amygdalae and sgACC ROIs. For the n-back task, we used our one contrast of interest (3-back>1-back) to extract the average parameter estimate for the left and right DLPFC ROIs. We analysed these average ROI values using mixed ANOVAs in SPSS. We tested for any associations between these average ROI values and symptom measures (depression (BDI), anxiety (BAI), and anhedonia (SHAPS)). In line with our predictions about the interaction between cold and hot cognitive mechanisms, we also tested for an association between DLPFC activation during cold cognition and amygdala or sgACC activation during hot cognition.

For our secondary exploratory analyses, we performed a whole-brain one-way ANOVA (using an F-test) for the effect of group in SPM (cluster forming threshold $p<0.001$ uncorrected). For the n-back task, the F-test was performed on the 3-back>1-back contrast. For the faces task, we performed the F-test on all three contrasts: the two contrasts of interest, and the faces>fixation contrast.

4.3.4 Power analyses

To determine our sample size, we ran power analyses separately for each region using G*Power 3.1.9.2; F-tests; ANOVA: repeated measures, between factors, $\alpha = 0.05$). In both cases, we expected to find a moderate effect size (Cohen's *d* of 0.5 to 0.6), as previous studies have shown effect sizes of 0.58 and 0.83 for the right and left amygdala, respectively (comparing healthy controls and an at-risk sample during emotional face processing (Monk et al., 2008)) and up to 1.85 for the left DLPFC (comparing healthy controls and depressed patients on the n-back task (Wang et al., 2015)).

The DLPFC and sgACC each had two repeated measurements (for the DLPFC: left and right DLPFC; for the sgACC: fearful and neutral contrasts). For these regions, a three-group study with two moderately-correlated (0.5) repeated measurements required 24-33 participants per group to achieve 80% power with an assumed effect size of 0.5-0.6. For a three-group study with four repeated measurements, as in the amygdala (left/right; fearful/neutral), we needed between 21 and 30 people to achieve 80% power, again assuming an effect size between 0.5 and 0.6.

Similar sample sizes were obtained for *a priori* power calculations for correlation analyses within the depressed group (i.e., relationship between activation in each region and symptom measures). A previous study found a moderate effect size (r=0.63) for the relationship between amygdala responsivity and BDI scores in patients with depression (Hamilton and Gotlib, 2008). However, we have previously identified smaller effect sizes (r=0.36) for the relationship between anhedonia (SHAPS) and activation in another subcortical structure, the habenula, in patients with depression (Lawson et al., 2016). Using an intermediate effect size of r=0.45 (correlation tests: point biserial model), we calculated that we required 33 subjects to achieve 80% power. However, for smaller effects (e.g., r=0.3), we would have required 82 subjects per group. Therefore, our study did not have the power to detect more subtle correlations between symptoms and neural activation.

4.4 Results

4.4.1 Clinical, demographic and behavioural data

In one-way ANOVAs with group as the between-subjects factor, there was no effect of group on age or FSIQ (both $p>0.1$); a chi-square test also revealed no effect of

group on sex (X^2=0.734, p=0.693). There were significant effects of group on HAM-D (F(2,96)=828.19, p<0.001), BDI (F(2,96)=346.61, p<0.001), SHAPS (F(2,96)=64.01, p<0.001), and BAI scores (F(2,96)=72.55, p<0.001). Post-hoc linear comparisons showed that healthy controls did not differ significantly from first-degree relatives on any measure (all p>0.05), but differed from depressed patients on all clinical scales: HAM-D (t(67)=20.47, p<0.001), BDI (t(67)=25.88, p<0.001), BAI (t(67)=22.59, p<0.001), and SHAPS (t(67)=13.61, p<0.001). First-degree relatives also differed from depressed patients on all clinical measures (HAM-D (t(67)=30.20, p<0.001), BDI (t(67)=19.06, p<0.001), BAI (t(67)=8.60, p<0.001), and SHAPS (t(67)=9.25, p<0.001)). See Table 4.2 for full participant characteristics of each group.

Accuracy data collected in the scanner did not conform to assumptions of normality (Komolgorov-Smirnov test: for the n-back task, d'=0.123, p=0.001; for the emotion processing task, d'=0.266, p<0.001). To test for an effect of group, we therefore conducted nonparametric Kruskal-Wallis tests, which did not reveal any group differences in d' for the n-back task (p=0.149, controls: M=2.03 SD=0.93; relatives: M=1.85, SD=0.98; patients: M=1.56, SD=0.87) or accuracy at gender classification during the emotion processing task: p=0.102, controls: M=96.4% SD=1.04; relatives: M=96.6%, SD=0.60; patients: M=97.3%, SD=0.90).

Reaction time data conformed to assumptions of normality (Komolgorov-Smirnov tests, p>0.05). To test for an effect of group on n-back reaction times (correct responses only), we conducted a one-way ANOVA, finding no effect of group (F(2,97)=1.51, p=0.227). For the emotion processing task, we conducted a repeated-measures ANOVA with the within-subjects factor emotion (happy, fearful, or neutral

faces), finding no main effect of emotion ($F(2,192)=0.768$, $p=0.466$), interaction with group ($F(4,192)=0.564$, $p=0.689$) or effect of group ($F(2,96)=1.35$, $p=0.263$).

	Controls	Relatives	Patients
N	30	30	39
% F	50	60	51
Age	32.10 (8.68)	28.67 (8.40)	33.38 (10.97)
FSIQ	110.54 (0.91)	109.73 (0.93)	107.30 (1.62)
HAM-D	1.17 (1.47)	2.40 (4.95)	21.64 (3.30) *
BDI	1.53 (2.15)	1.86 (3.09)	27.41 (6.76) *
SHAPS	5.37 (5.21)	5.07 (4.93)	18.97 (9.09) *
BAI	3.00 (4.21)	4.17 (5.84)	25.59 (12.69) *
Age onset	n/a	n/a	19.97 (9.09)
No. episodes	n/a	n/a	2.77 (1.63)
% first-degree relative w/ MDD	0	100	46.15
% attempted suicide	n/a	n/a	31
% past ADM	n/a	n/a	41
% past PT	n/a	n/a	64

Table 4.2 Participant characteristics. F = female; FSIQ = Full Scale Intelligence Quotient; HAM-D = Hamilton Rating Scale for Depression; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory; SHAPS = Snaith Hamilton Pleasure Scale; No. = number; MDD = Major Depressive Disorder; % past ADM = per cent of patients with any previous history antidepressant medication use (no patients were currently-medicated: see Methods); % past PT = per cent of patients with a history of psychological therapy; * *F*-test $p<0.05$ for effect of group.

4.4.2 fMRI results

We first report whole-brain activation for both tasks, collapsing across all groups for all contrasts and their respective inverses. We then test for group differences in average activation across our *a priori* ROIs for our contrasts of interest only. Lastly, we report the results of whole-brain F-tests for group differences (using a cluster-forming threshold of $p<0.001$ uncorrected).

4.4.2.1 Activation across groups: n-back task

The effect of high vs low working memory condition (3-back versus 1-back; whole-brain $p<0.05$, voxel-level FWE-corrected) evoked very large clusters of activation extending from a peak in the insula to the bilateral DLPFC, as well as several significant clusters elsewhere, including a large cluster with a peak in the posterior parietal cortex (see Table 4.3). The inverse contrast evoked substantial VMPFC and posterior cingulate activation. An anatomical mask including Brodmann areas 9 and 46 confirmed substantial activation in the left and right DLPFC in the 3-back<1-back contrast (see Table 4.4).

Contrast	*p* (cluster-corrected)	Extent	*p* (voxel-corrected)	t(97)	X	Y	Z	region
3-back > 1-back	<0.001	4561	<0.001	12.36	33	20	-1	insula, DLPFC
	<0.001	289	<0.001	12.24	30	-64	-31	R cerebellum
	<0.001	2073	<0.001	10.99	42	-43	44	R PPC
	0.001	17	<0.001	7.54	57	-52	-10	R fusiform
	<0.001	63	<0.001	6.52	-12	-4	2	L thalamus
	<0.001	51	<0.001	6.28	15	-4	-1	R thalamus
	0.017	2	0.002	5.70	3	14	23	R mid-cingulate
	0.017	2	0.009	5.29	0	-52	-16	cerebellum
	0.026	1	0.014	5.18	-21	47	-10	L VMPFC
	0.026	1	0.030	4.97	57	-34	-13	lat. temporal
1-back > 3-back	<0.001	1430	<0.001	13.20	-3	29	-19	L VMPFC
	<0.001	8026	<0.001	11.30	-9	-52	11	L posterior cingulate cortex
	0.013	3	0.006	5.39	54	35	2	R VLPFC
	0.026	1	0.030	4.97	24	11	-10	R putamen
	0.026	1	0.032	4.94	15	-28	-1	R thalamus
	0.026	1	0.045	4.85	12	-31	5	R thalamus

Table 4.3 Whole brain activation results: n-back task. Whole-brain significant activation during n-back task, for the 3-back>1-back contrast and its inverse, 1-back>3-back (cluster-forming threshold $p<0.05$, voxel-level FWE corrected). BA=Brodmann area; L=left; R=right. DLPFC=dorsolateral prefrontal cortex; PPC=posterior parietal cortex; VMPFC=ventromedial prefrontal cortex; VLPFC=ventrolateral prefrontal cortex; lat.=lateral.

Contrast	*p* (cluster-corrected)	Extent	*p* (voxel-corrected)	t(97)	X	Y	Z	region
3-back > 1-back	<0.001	91	<0.001	9.72	-45	11	32	L DLPFC
	<0.001	8	<0.001	8.47	-6	29	38	L DLPFC
	<0.001	29	<0.001	7.72	-45	29	23	L DLPFC
	0.001	1	<0.001	6.68	-42	50	17	L DLPFC
	0.001	1	<0.001	5.18	-9	35	29	L DLPFC
	<0.001	41	<0.001	10.51	45	41	23	R DLPFC
	<0.001	94	<0.001	9.57	42	32	35	R DLPFC
	<0.001	23	<0.001	9.41	3	29	38	R DLPFC
	0.017	2	<0.001	9.15	42	50	20	R DLPFC
	0.006	6	<0.001	7.54	33	41	29	R DLPFC
	0.007	5	0.002	5.72	51	23	26	R DLPFC

Table 4.4 DLPFC activation: n-back task. Small volume (SV)-corrected activation for the contrast of interest in the n-back task, using a separate anatomical mask for left (L) and right (R) dorsolateral prefrontal cortex (DLPFC, here including Brodmann area 9 and Brodmann area 46) for the 3-back>1-back contrast (cluster-forming threshold $p<0.05$, voxel-level FWE corrected). DLPFC=dorsolateral prefrontal cortex.

4.4.2.2 Activation across groups: faces task

In the emotion processing task, the effect of fearful (versus neutral) faces (whole-brain $p<0.05$, voxel-level FWE-corrected) evoked bilateral activation in the fusiform gyri, as well as a large cluster in the lateral temporal cortex, and a cluster in the ventrolateral prefrontal cortex. There were no whole-brain significant results for the inverse contrast, or for the effect of happy (versus neutral) faces (or its inverse) at this threshold. The effect of faces in general (versus the fixation cross baseline) evoked widespread activation, including large clusters in the visual associative area, hippocampus, supplementary motor area, and orbitofrontal regions. The inverse contrast also evoked distributed activation, with the largest clusters in the sgACC and posterior cingulate, and smaller ones in sensory, parietal, and temporal regions. See Table 4.5 for all whole-brain results.

We explored whether significant activation was present in our *a priori* ROIs using a small-volume correction (SVC) for anatomical masks of the amygdalae and sgACC

(cluster-forming threshold $p<0.001$, uncorrected; see Table 4.6) for each contrast and its inverse. As expected from our whole-brain results, the effect of all faces vs fixation evoked significant activation in the bilateral amygdalae, and its inverse (fixation>faces) evoked significant activation in the sgACC. The fearful>neutral contrast also yielded significant activation in the bilateral amygdalae. The inverse emotion-specific contrasts (and the happy>neutral contrast) did not yield significant activation in any of our ROIs at this threshold.

Contrast	p (cluster level)	Extent (k)	p (voxel level)	t(98)	X	Y	Z	region
fearful>neutral	<0.001	233	<0.001	7.56	51	-37	5	R lateral temporal
	<0.001	39	<0.001	6.84	-42	-52	-16	L fusiform
	<0.001	26	<0.001	6.26	45	-43	-16	R fusiform
	<0.001	22	<0.001	5.88	54	32	2	R VLPFC
	<0.001	45	0.001	5.83	-51	-49	5	L lateral temporal
	<0.001	12	0.004	5.49	51	14	-19	R temporal pole
	0.010	4	0.020	5.06	30	-94	5	R vis. assoc.
neutral>fearful	none							
happy>neutral	none							
neutral>happy	none							
faces>fixation	<0.001	5558	<0.001	26.85	36	-85	-7	R vis. assoc.
	<0.001	2571	<0.001	15.17	-24	-31	-1	L hipp.
	<0.001	491	<0.001	9.36	-39	-1	17	L premotor cortex
	<0.001	104	<0.001	8.74	-6	8	50	L SMA
	<0.001	138	<0.001	7.77	-39	-28	41	L parietal
	<0.001	34	<0.001	7.7	3	44	-22	R OFC
	<0.001	65	<0.001	6.89	30	35	-19	R VLPFC
	<0.001	18	<0.001	5.52	0	14	11	Bilateral caudate
	0.010	4	<0.001	5.48	-39	47	29	L rostral PFC
fixation>faces	<0.001	2493	<0.001	14.66	9	44	-4	sgACC
	<0.001	1685	<0.001	14.4	-12	-64	20	L post.cingulate
	<0.001	270	<0.001	11.13	27	29	38	R mPFC
	<0.001	654	<0.001	11.09	39	-19	17	R prim. sensory
	<0.001	414	<0.001	8.27	-54	-7	-13	L sup. temporal
	<0.001	73	<0.001	8.13	42	-16	41	R M1
	<0.001	49	<0.001	7.01	-57	-58	26	L parietal
	<0.001	33	<0.001	6.66	60	-58	26	R inferior parietal
	<0.001	12	<0.001	6.38	-60	-55	-7	L fusiform
	0.001	4	0.020	5.06	18	50	23	R rostral PFC

Table 4.5 Whole brain activation results: emotion processing task. Whole brain activation (cluster-forming threshold $p<0.05$, FWE-corrected). R=right; L=left. VLPFC=ventrolateral prefrontal cortex; OFC=orbitofrontal cortex; mPFC=medial prefrontal cortex; SMA=supplementary motor area; sgACC=subgenual anterior cingulate cortex; vis. assoc.=visual associative; prim.=primary; sup.=superior; M1=primary motor cortex. Both cluster-level and voxel level *p*-values are whole-brain FWE corrected.

Contrast	*p* (cluster-corrected)	Extent	p (voxel-corrected)	t(98)	X	Y	Z	region
happy>neutral	0.989	1	0.849	3.66	3	41	2	sgACC
	0.989	1	0.969	3.43	0	14	-7	sgACC
	0.989	1	0.996	3.22	-3	29	4	
neutral>happy	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
fearful>neutral	0.002	28	<0.001	4.71	-30	-1	-19	L Amyg
	0.004	16	0.001	4.31	30	2	-22	R Amyg
neutral>fearful	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
faces>fixation	0.001	38	<0.001	9.98	-24	-7	-13	L Amyg
	<0.001	51	<0.001	9.24	27	-4	-19	R Amyg
fixation>faces	<0.001	299	<0.001	13.82	9	38	-7	sgACC

Table 4.6 Amygdala and sgACC activation: faces task. SV-corrected activation for all contrasts in the faces task using separate anatomical masks for the subgenual anterior cingulate cortex (sgACC), and right (R) and left (L) amygdalae (Amyg) (cluster-forming threshold $p<0.001$, uncorrected).

4.4.2.3 Group differences in DLPFC activation during working memory (average over ROI)

We extracted average activation from each DLPFC ROI for each subject (n-back task: 3-back>1-back contrast). The extracted average activation met assumptions of normality (Komolgorov-Smirnov test, both $p>0.05$). We conducted a repeated-measures ANOVA, with a within-subjects factor of laterality and a between-subjects factor of group. We initially included sex and age in the model, but found no significant main or interaction effects of either variable (all $p>0.3$), so we excluded both from subsequent models. We found a significant effect of group on DLPFC activation ($F(2,95)=4.55$, $p=0.013$, $\eta_p^2=0.087$), as well as stronger activation in the left than the right DLPFC ($F(1,95)=8.08$, $p=0.005$, $\eta_p^2=0.078$). The laterality-by-group interaction was non-significant ($F(2,95)=0.296$, $p=0.744$). Post-hoc analysis (least-squared difference (LSD) tests) revealed that patients had significantly lower DLPFC activation compared to both unaffected relatives (*mean difference*=0.169, $p=0.007$, Cohen's $d=0.674$) and healthy controls (*mean difference*=0.162, $p=0.024$, Cohen's $d=0.560$). There were no differences between DLPFC activation in controls and

unaffected relatives (*mean difference*=0.006, *p*=0.923). See Figure 4.1 for distribution and mean of average DLPFC contrast estimates.

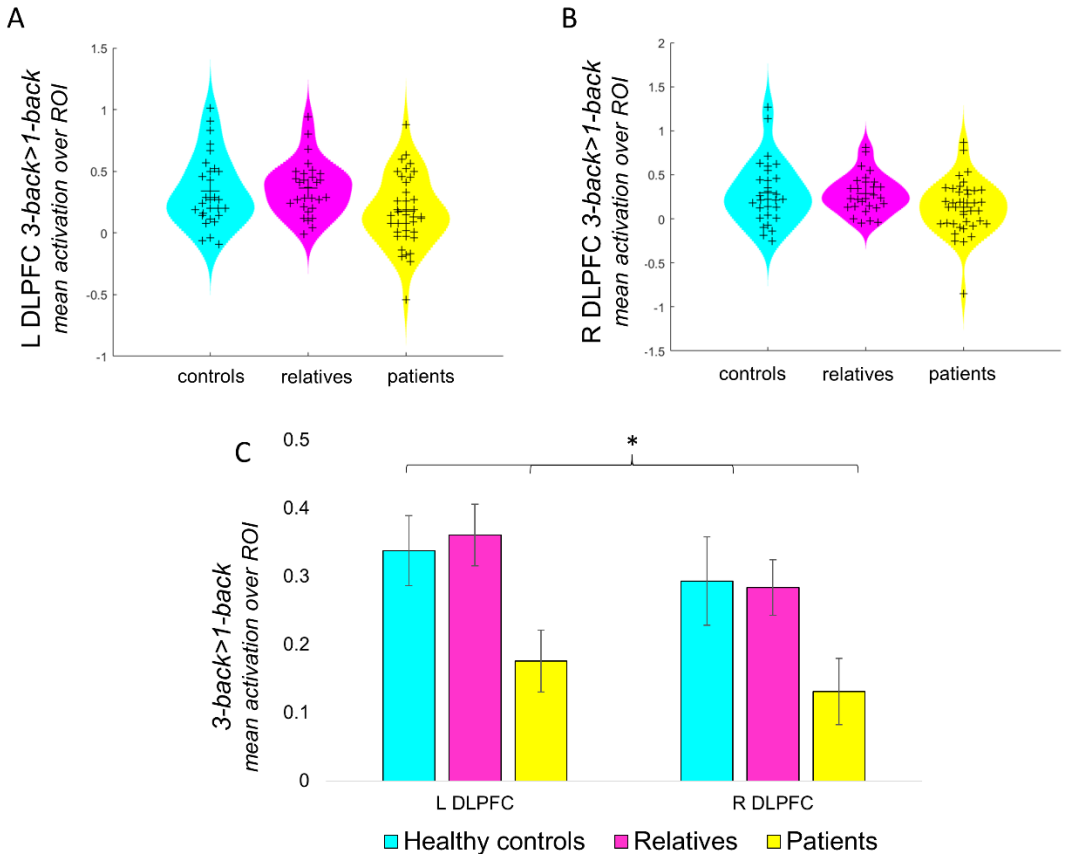

Figure 4.1 Distribution and mean of average DLPFC contrast estimates. A-B: Distribution of means ((+) represents one subject in the left (A) and right (B) DLPFC ROIs). C: Mean contrast estimate across each DLPFC ROI for each group. In 4.1C, (*) indicates a significant main effect of group (*p*=0.010). There was also a significant main effect of laterality (*p*=0.004). L=left; R=right; DLPFC=dorsolateral prefrontal cortex. Error bars represent standard error of the mean.

4.4.2.4 Correlations with DLPFC in the depressed sample

There was a much wider distribution of self-report symptoms in the patients' questionnaire responses than in the other groups (see Table 4.1). For this reason, we explored associations between depressive symptoms and mean DLPFC activation only in the patient group. All questionnaire measures met assumptions of normality (Kolmogorov-Smirnov test, all *p*>0.2). We employed eight parametric Pearson correlations to test associations between our four symptom measures

(depression (BDI and HAM-D), anhedonia (SHAPS), and anxiety (BAI)) and DLPFC activation (Bonferroni-corrected p=0.0063) and each DLPFC. We did not find any significant associations even at a nominally significant level (all p>0.1).

4.4.2.5 Group differences in amygdala activation during emotion processing (average over ROI)

All but two average parameter estimates for the amygdala met the assumption of normality (Kolmogorov-Smirnov test, all p>0.2). In the two that did not (amygdala activation in the fearful>neutral faces contrast: left: p=0.049; right: p=0.036), we performed two nonparametric independent samples Kruskal-Wallis tests to confirm the results of the ANOVA. We conducted a repeated-measures ANOVA, with within-subjects factor of emotion (fear, happy) and laterality, and between-subjects factor of group. We initially included sex and age in the model, but found no significant main or interaction effects of either variable (all p>0.2); therefore, neither were included in our model. Amygdala activation for the fearful>neutral contrast was significantly stronger than for the happy>neutral contrast (F(1,96)=17.05, p<0.001, η_p^2=0.151). There was no significant effect of laterality (F(1,96)=0.513, p=0.476) or significant interaction between laterality and group (F(2,96)=0.079, p=0.924) (see Figure 4.2). There was no significant interaction between emotion and laterality (F(1,96)=0.088, p=0.767) or between emotion, group, and laterality (F(2,96)=1.325, p=0.271).

We did not find a significant effect of group (F(2,96)=0.538, p=0.586), which was confirmed by the two non-parametric independent samples Kruskal-Wallis test in the amygdala fearful faces contrasts (left: p=0.573, right: p=0.916); the interaction between group and emotion was also not significant (F(1,96)=2.28, p=0.108). See

Figure 4.2 for distribution and means of activations across contrasts in each amygdala.

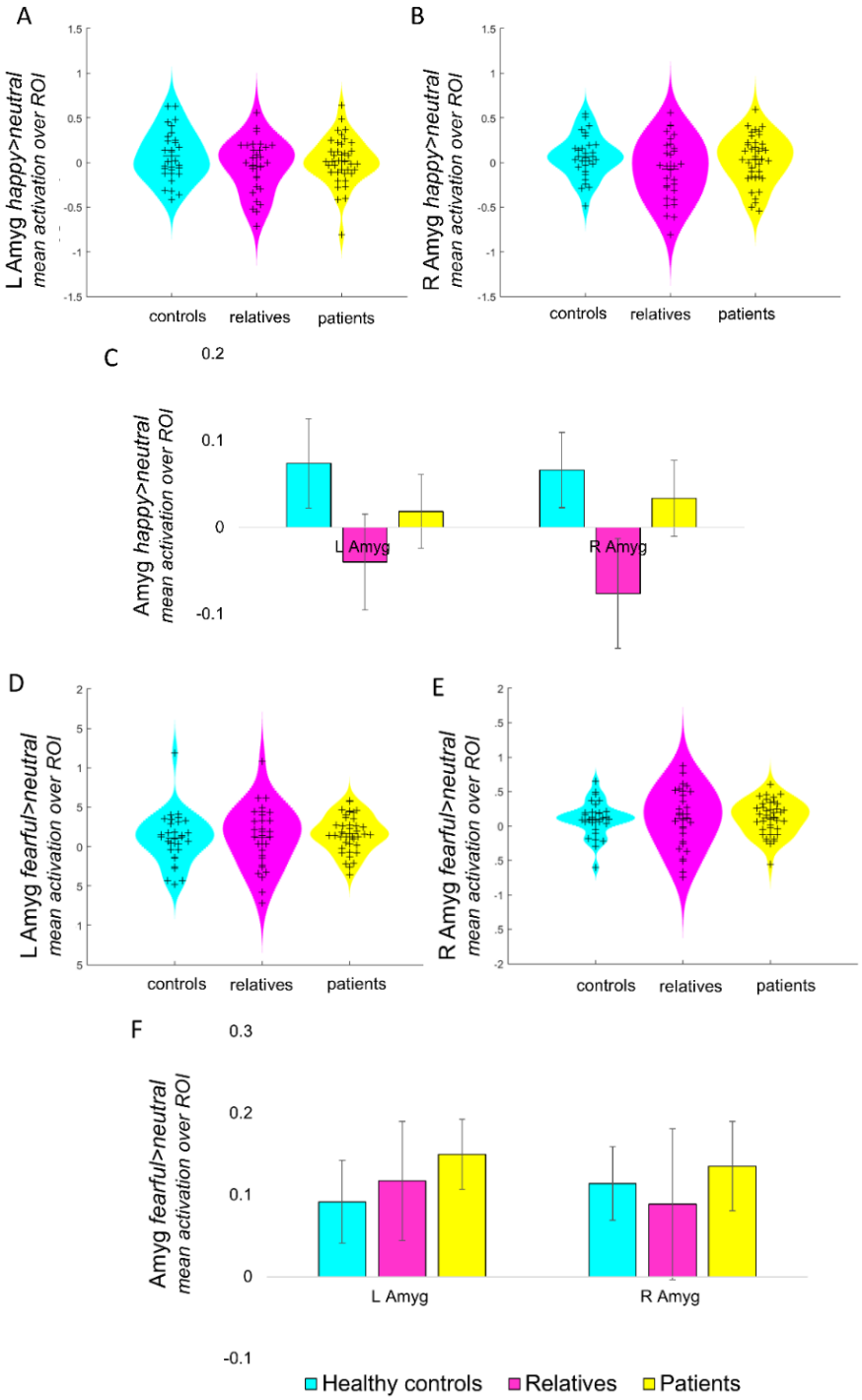

Figure 4.2 Distribution and mean of average amygdala contrast estimates. A-B: Distribution of means ((+) represents one subject in the left (A) and right (B) amygdala) for the happy>neutral contrast. C: Mean contrast estimate across each amygdala ROI for the happy>neutral contrast. D-E: Distribution of means ((+) represents one subject in the left (D) and right (E) amygdala) for the fearful>neutral contrast. F: Mean contrast estimate across each amygdala ROI for the fearful>neutral contrast. L=left; R=right; Amyg=amygdala. Error bars represent standard error of the mean.

4.4.2.6 Correlations with amygdala activation in the depressed sample

We explored in the patient group whether there was any association between depressive symptoms and amygdala activation (averaged across both amygdalae; separately for each emotion). As before, we calculated eight Pearson correlation coefficients (for each questionnaire measure). No correlations were nominally significant (corrected significance threshold: p=0.0063; all p>0.05).

4.4.2.7 Group differences in sgACC activation during emotion processing (average over ROI)

For the sgACC, all average parameter estimates met the assumption of normality (Kolmogorov-Smirnov test, all p>0.2). We conducted a repeated-measures ANOVA, with a within-subjects factor of emotion (fear, happy), and the between-subjects factor of group. We initially included sex and age in the model, but found no significant main or interaction effects of either (all p>0.2), therefore, neither were included in our model. We found no significant main effect of group (F(2,96)=0.105, p=0.900) (see Figure 4.3). The happy>neutral contrasts evoked significantly larger activation than the fearful>neutral contrast (F(1,96)=5.09, p=0.026), but there was no significant emotion-by-group interaction (F(2,96)=0.249, p=0.780).

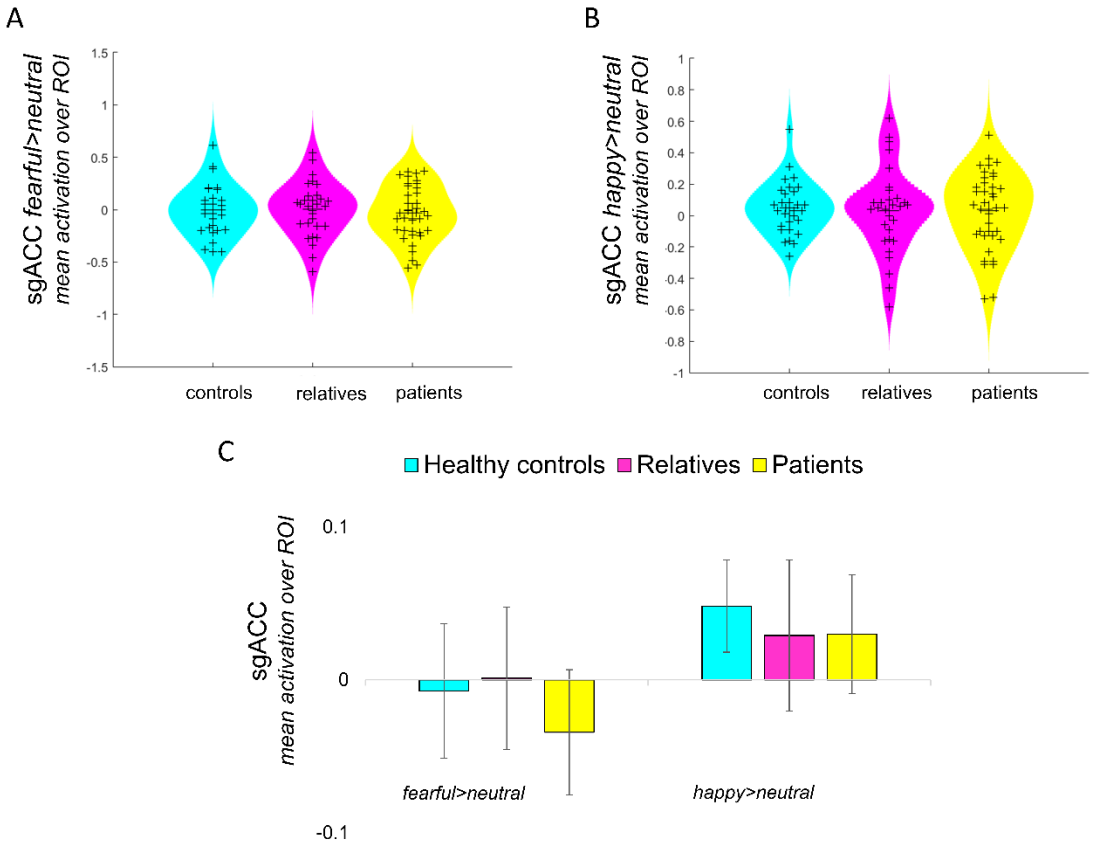

Figure 4.3 Distribution and mean of average sgACC contrast estimates. A-B: Distribution of means ((+) represents one subject) for the fearful>neutral (A) and happy>neutral (B) contrasts for the sgACC. C: Mean contrast estimate across the sgACC for both contrasts. sgACC=subgenual anterior cingulate cortex. Error bars indicate standard error of the mean.

4.4.2.8 Correlations with sgACC activation in the depressed sample

We explored in the patient group whether there was any association between depressive symptoms and sgACC activation. We calculated eight Pearson correlation coefficients, for each emotion contrast. We found that sgACC activation to happy faces negatively correlated with both measures of depression at a nominally significant level: HAM-D (r=-0.348, p=0.030) and BDI (r=-0.317, p=0.049) (see Figure 4.4). Both indicated that lower sgACC responses (i.e., more deactivation to emotional faces) were associated with higher levels of depressive symptoms. Bonferroni correction for multiple comparisons yielded a significance threshold of p=0.0063; thus, both missed significance at the corrected threshold. In the case of sgACC activation to fearful faces, neither HAM-D nor BDI scores correlated with

activation (HAM-D (r=-0.284, p=0.080) and BDI (r=-0.302, p=0.062)), though both were marginally significant in the same direction: lower sgACC responses corresponded with higher levels of depression. There were no associations with anxiety (BAI) or anhedonia (SHAPS) scores for sgACC responses to either happy or fearful faces, (all p>0.4).

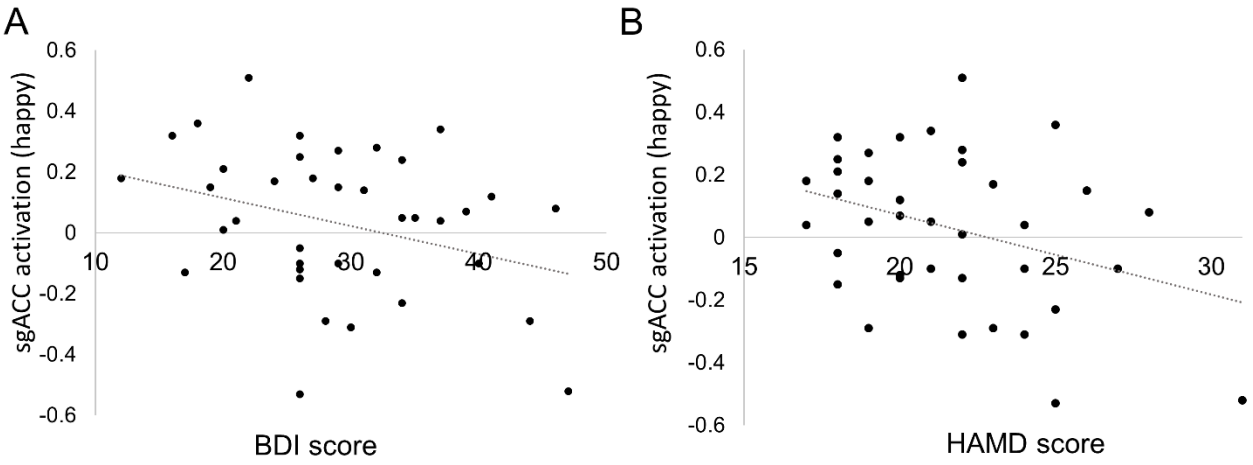

Figure 4.4 Association between sgACC activation and depression scores. Relationship between subgenual anterior cingulate cortex (sgACC) activation to happy faces and symptom scores in depressed patients for Beck Depression Inventory (BDI, p=0.049, non-significant at corrected threshold of p=0.0063, A) and Hamilton Depression rating scale (HAM-D, p=0.030, non-significant at corrected threshold of p=0.0063, B).

4.4.2.9 Correlations between activation evoked during working memory and emotion processing

We tested across all participants whether there was an association between left or right DLPFC activation during the n-back task and activation in the amygdala (collapsed across left and right) or sgACC, separately during fearful and happy faces (N=98; 8 correlations). There was a nominally significant negative relationship between right DLPFC activation (during the n-back task) and amygdala activation to happy faces, r=-0.237, p=0.019, such that participants with the highest DLPFC activation had the lowest amygdala activation during happy faces (see Figure 4.5). However, this was not significant after applying Bonferroni correction for multiple

comparisons (corrected significance threshold: p=0.0063). No other correlations met criteria for nominal significance (all p>0.1).

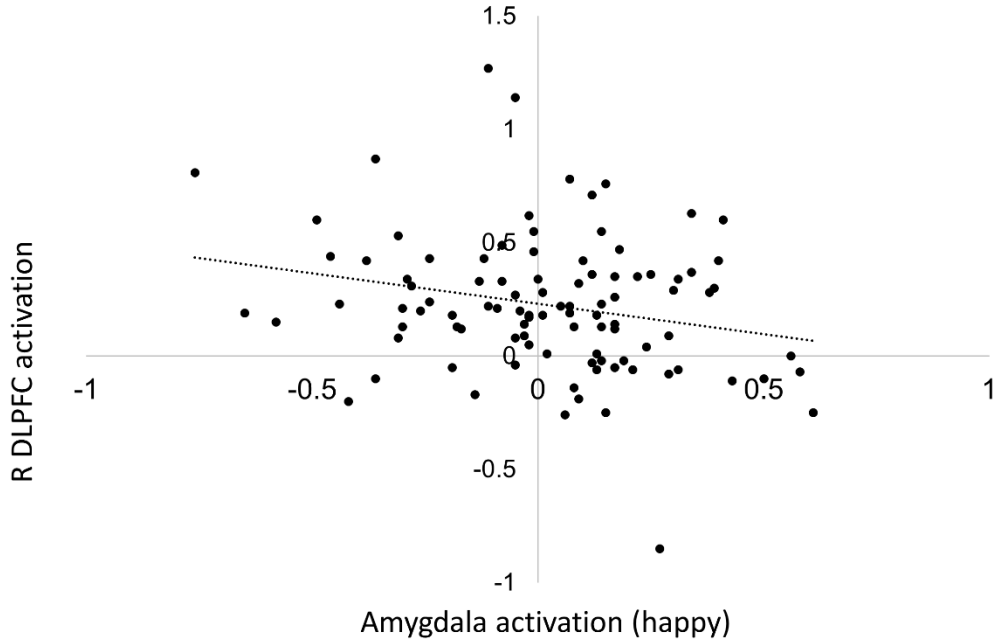

Figure 4.5 Association between amygdala and DLPFC activation. Correlation between amygdala activation to happy faces (average across left and right) and right dorsolateral prefrontal cortex (R DLPFC) activation during the n-back task (r=-0.237, p=0.019, non-significant at corrected threshold of p=0.0063).

4.4.2.10 Whole-brain group differences: n-back task

In each task, for each contrast, we also ran an exploratory whole-brain ANOVAs (F-test) in SPM to test for group differences.

In the n-back task, no group differences survived whole-brain FWE correction (either cluster- or voxel-level). For completeness, we report all results exceeding a threshold of p<0.001 (uncorrected) in Table 4.7. Employing a SV correction using a bilateral DLPFC anatomical mask, the L DLPFC cluster did not survive FWE correction (either cluster- or voxel-level); for completeness, all SV-corrected results exceeding a threshold of p<0.001 (uncorrected) are reported in Table 4.8.

Contrast	p (cluster-corrected)	Extent	p (voxel-corrected)	F(2,95)	X	Y	Z	region
3-back> 1-back	0.978	3	0.981	8.55	-12	-13	47	Mid-cingulate
	0.990	2	0.982	8.54	15	-10	35	dACC
	0.990	2	0.990	8.32	-21	32	-7	L VLPFC
	0.848	8	0.995	8.12	-45	20	29	L DLPFC
	0.978	3	0.997	7.99	36	23	-7	R insula
	0.997	1	0.998	7.84	36	-37	-10	R hippocampus
	0.990	2	0.999	7.72	-15	-85	-22	L cerebellum
	0.997	1	0.999	7.67	-42	-1	32	L premotor
	0.990	2	0.999	7.64	-27	-34	8	L thalamus
	0.997	1	0.999	7.63	27	-40	-1	R hippocampus
	0.997	1	0.999	7.58	-39	17	14	L VLPFC

Table 4.7 Whole brain group differences: n-back task. Whole brain group differences on the n-back task (p<0.001 uncorrected). Note: the F-test tests for effects in both directions (i.e., the contrast and its inverse). L=left; DLPFC=dorsolateral prefrontal cortex; dACC=dorsal anterior cingulate cortex; VLPFC=ventrolateral prefrontal cortex.

Contrast	p (cluster-corrected)	Extent	p (voxel-corrected)	F(2,95)	X	Y	Z	region
3-back> 1-back	0.530	1	0.624	7.59	-45	17	26	L DLPFC

Table 4.8 SVC group differences: n-back task. SVC group differences on the n-back task (p<0.001 uncorrected). Note: the F-test tests for effects in both directions (i.e., the contrast and its inverse). L=left; DLPFC=dorsolateral prefrontal cortex.

4.4.2.11 Whole-brain group differences: faces task

There were no whole-brain significant differences in the emotion processing task in the three ROIs (amygdalae and sgACC), corrected for 3 ROIs. For completeness we report all results exceeding a threshold of p<0.001 (uncorrected) in Table 4.9. Employing a SV correction using anatomical masks of each ROI (amygdalae and sgACC), there were no clusters that survived, using either cluster- or voxel-correction.

Contrast	*p* (cluster-corrected)	Extent	*p* (voxel-corrected)	F(2,96)	X	Y	Z	region
faces>baseline	0.201	26	0.695	10.32	-42	-64	-31	L cerebellum
	0.995	1	0.996	8.03	21	-22	38	WM
	0.995	1	0.999	7.72	-33	-52	17	L parietal
fearful>neutral	0.951	4	0.959	12.83	-27	-16	20	L dorsal thalamus
	0.986	2	0.188	8.76	-3	-34	-43	L pons
happy>neutral	0.969	3	0.733	10.11	-36	-25	26	L prim. sensory
	0.997	1	0.999	8.65	15	-34	11	R dorsal thalamus
	0.990	2	0.980	7.74	6	-22	-16	Midbrain

Table 4.9 Whole brain group differences: emotion processing task. Whole brain group differences on the emotion processing task (p<0.001 uncorrected). Note: the F-test tests for effects in both directions (i.e., the contrast and its inverse). R=right; L=left; prim.=primary; WM=white matter.

4.5 Discussion

We report results from a relatively large three-group fMRI study, comparing neural activation in unmedicated patients with depression, unaffected first-degree relatives of depressed patients, and healthy controls. We probed two different circuits: dorsal prefrontal (cold, executive function), using an n-back working memory task, and ventral prefrontal/subcortical (hot, emotion processing), using an incidental emotion task. We found that unaffected first-degree relatives show intact dorsolateral prefrontal cortex activation during working memory processing, while depressed patients show hypoactivation in the DLPFC, compared with healthy controls. However, we failed to detect any group differences in the emotion processing task.

Our findings support a large literature of DLPFC abnormalities in depression (Baxter et al., 1989; Bench et al., 1993; Drevets, 1999; Harvey et al., 2005; Siegle et al., 2007a; Wagner et al., 2006; Walter et al., 2007; Wang et al., 2015). Few studies have directly probed this region in unaffected first-degree relatives of depressed patients. One report found diminished DLPFC responses to the presentation of fearful faces in first-degree relatives of depressed patients, but in this sample first-degree relatives showed higher depressive symptoms than controls (Mannie et al., 2011). By contrast, in our study, there were no differences in any symptom measure between first-degree relatives and healthy controls. Therefore, it is possible our sample reflects a more resilient group than previous ‘at-risk’ samples. Our report of intact DLPFC activity during working memory in those with a familial risk for depression may represent a protective factor in at-risk populations. To test this, future research might better characterise first-degree relatives using polygenic risk scores: a recent study found healthy controls with high polygenic risk scores for

depression showed lower activation in fronto-parietal brain areas in the n-back task (resembling our patient group) than those with a low polygenic risk score (Yüksel et al., 2017).

On the other hand, we did not find any group effect on sgACC or amygdala responsivity to emotional faces. Previous studies have shown aberrant neural activation during hot cognitive processing in first-degree relatives, compared to healthy controls (Chan et al., 2009; Monk et al., 2008; Olsavsky et al., 2012; Surguladze et al., 2010), though this has not always been reported (Mannie et al., 2011). Drawing on this work, as well as the cognitive neuropsychological model of depression, we predicted that depressed patients, and possibly unaffected relatives, would show aberrant sgACC and amygdala responses to fearful faces compared to healthy controls. Our data did not support this prediction. However, in the case of sgACC responses, there is notable individual variation in activation within depressed patients. In a large prospective study, baseline sgACC activation (in response to negative words) predicted response to cognitive therapy (Siegle et al., 2012): patients with lower sgACC activation relative to healthy controls showed a stronger therapeutic response than those with higher sgACC activation. Thus, it is possible that heterogeneity within our patient sample may have obscured any group differences. In tentative support of this, we found sgACC deactivation to happy faces was weakly associated with lower depression scores, on both interviewer (HAM-D) and self-report (BDI) measures of depression in the patient group; however, these correlations did not survive correction for multiple comparisons.

4.5.1 Relationship between executive control and emotion processing

Although we investigate executive control and emotion processing separately here, these mechanisms interact strongly with one another in the aetiology of depressive symptoms. For instance, the DLPFC is thought to regulate emotions via inhibition of limbic regions such as the amygdala (Davidson et al., 2003; Mayberg et al., 1999; Ochsner et al., 2002, 2004). Thus, emotional reactivity (and corresponding neural abnormalities in the limbic circuit) could in part originate through inefficient frontal mechanisms. In support of this idea, both healthy individuals (Dolcos and McCarthy, 2006) and depressed patients (Siegle et al., 2002) show amygdala hyperactivation that is linked to decreased DLPFC activation (Siegle et al., 2007a). We found that higher amygdala activation (during happy emotion processing) was weakly associated with lower DLPFC activation (in the n-back task) across all subjects. Again, however, this association did not survive correction for multiple comparisons. Additionally, we did not observe even a nominally significant correlation for the equivalent correlation with fearful faces, which casts some doubt on this result.

4.5.2 Limitations

Our study included a moderately large sample size (N=99), and probed the role of two separate cognitive and neural processes in risk and resilience for depression. Our power analysis indicated this sample was sufficient to detect a small-to-moderate effect of group. However, a larger sample size would be needed to detect more subtle relationships between brain activation and symptom measures, as our previous work has found these to be relatively weak (Lawson et al., 2016). We identified two correlations between depressive symptoms and sgACC activation, but neither survived Bonferroni correction for multiple comparisons; similarly, a

preliminary relationship between amygdala and DLPFC activation across the two tasks did not survive Bonferroni correction. It is also possible that a larger sample size might yield group differences in the emotion processing task, since differences in emotion processing between depressed patients and healthy controls are well-replicated, and inclusion of the third group may have masked any overall group effect. This would be particularly helpful in the depressed group, already our largest sample (N=39), but whom we might expect to show the largest variability in sgACC responses (Siegle et al., 2012).

4.5.3 Future directions and conclusion

It is important to understand the deviations in neural circuitry conferring risk or resilience for psychiatric disorders. A better understanding of neural risk factors could clarify the mechanisms of successful treatment, or even shed light on ways to prevent symptoms in the first place. For instance, working memory training in dysphoric patients using the n-back task resulted in improved working memory capacity, with concomitant increases in the neural filtering of irrelevant information (measured using electroencephalography, EEG) (McGuffin et al., 1991). In older adults particularly, an important predictor of antidepressant response is executive dysfunction (Alexopoulos et al., 1997). Improving executive control might represent one way of treating or preventing depression, through top-down control of emotional processing regions. Studies are beginning to explore this possibility: several trials found unexpectedly that cognitive training in dementia improved depression symptoms (Davis et al., 2001; Loewenstein et al., 2004; Sitzer et al., 2006).

There have been two treatments developed specifically to target executive dysfunction in geriatric depression: computerized cognitive therapy (CCT) (Motter et

al., 2016) and problem-solving therapy (Arean et al., 1993). Both show effects on depression symptoms (Arean et al., 1993; Motter et al., 2015, 2016), though in a meta-analysis of 9 trials, CCT had an inconsistent effect on executive functioning itself (Motter et al., 2016). Nevertheless, cognitive training seems to have an effect on depression symptoms in patients with dementia; future trials should establish whether targeting executive symptoms is similarly effective in depressed patients without dementia (Roiser et al., 2012). An alternative approach involves directly targeting prefrontal mechanisms in depression with noninvasive brain stimulation. Transcranial magnetic stimulation (George et al., 2000) and transcranial direct current stimulation (Loo et al., 2012; Nord and Roiser, 2015) have both shown efficacy at treating depression; the latter in particular may work by targeting cold cognitive mechanisms in depression, as hypothesized in Chapter 3 (Metuki et al., 2012; Nord et al., 2017b). We test this last prospect in an RCT in Chapter 5.

Our findings provide novel insights about preserved dorsal prefrontal function in healthy participants with a family history of depression. This has important implications for understanding the neural basis of risk and resilience for major depression. Future work needs to better clarify the interaction between dorsal prefrontal and ventral prefrontal/subcortical responses in individuals at-risk for depression, with the view to preventing at-risk populations from developing depression, and better treating those who do.

Chapter 5. Neural, cognitive, and clinical effects of prefrontal cortex stimulation to enhance psychotherapy in depression: a double-blind randomized controlled trial

5.1 Abstract

Transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC) has recently shown efficacy as a treatment for depression. Here we combined tDCS with cognitive behavioural therapy (CBT) to determine whether DLPFC tDCS could enhance therapeutic outcome. We conducted a double-blind, sham-controlled, randomized controlled trial of tDCS in unmedicated depressed patients receiving a course of CBT (N=39). Patients received eight 20-minute sessions of either active or sham tDCS over the left DLPFC immediately before weekly CBT. The primary outcome was response (defined as >50% reduction in symptoms) on the Hamilton Rating Scale for Depression (HAM-D). Secondary outcomes included functional magnetic resonance imaging (fMRI) collected before and after the intervention during two paradigms, measuring neural responses elicited during working memory and emotion processing; weekly self-report symptoms; and weekly performance on the n-back working memory task. We also systematically assessed side-effects reported in each stimulation group. The intervention was relatively well tolerated, with 15% attrition (N=33 completers: 19 in the active group; 14 in the sham). Using an intent-to-treat analysis (last observation carried forward), more patients responded (active: 50%; sham: 31.6%; odds ratio: 2.16) and remitted

(active: 30%; sham: 10.5%; odds ratio: 3.65) following CBT with active than with sham tDCS; however, these differences did not achieve statistical significance: (response: X^2=1.37, p=0.12; remission: X^2=2.27, p=0.066). There were also no differences in working memory performance between active and sham conditions. We found a substantial increase in DLPFC activation during working memory following the intervention (using *a priori* ROIs, but also detectable at the whole-brain level), but this did not differ between active and sham tDCS conditions. However, during emotion processing, we found a group-by-time interaction for both amygdala and left DLPFC activation, such that activation generally decreased over the course of the study in both regions in the sham group, but increased in the active group from pre- to post-intervention.

The current findings provide support for the safety and tolerability of tDCS to augment CBT in depression. Additionally, they reveal some possible neural mechanisms associated with CBT (independent of tDCS effects) and tDCS interventions. However, they do not support a substantial clinical effect of tDCS combined with CBT for depression. These results have important implications for the clinical use of tDCS in depression: clinical response appears to be highly variable, and if an augmentative effect does exist it is likely to have a smaller effect size than initially anticipated. We discuss possible reasons for this variability in response, which may be due to the heterogeneity in the neural mechanisms of depression, as well as the lack of anatomical specificity in targeting the DLPFC with tDCS.

5.2 Introduction

Cognitive behavioural therapy (CBT) is a common, effective treatment for major depression (Churchill et al., 2002; Gloaguen et al., 1998). Nevertheless, only 60% of patients show an adequate response to therapy, and even fewer achieve remission (Rush et al., 2006). Some researchers have suggested enhancing CBT response with augmentative strategies, such as cognitive enhancing drugs (Frye et al., 2007), to improve outcome. More recently, noninvasive brain stimulation, including repetitive transcranial magnetic stimulation (rTMS) (Vedeniapin et al., 2010) and tDCS (D'Urso et al., 2013), has been suggested as an augmentative strategy to enhance response to CBT.

CBT is thought to target specific limbic and cortical brain regions, with CBT treatment, relative to antidepressant medication, in particular ameliorating several regional abnormalities in depression, including (measured at rest), the prefrontal cortex, cingulate, and hippocampus (Goldapple et al., 2004). However, some studies suggest that euthymic patients who have recovered from a major depressive episode continue to show persistent abnormalities, particularly in the DLPFC during high cognitive load tasks (Hooley et al., 2005; Kerestes et al., 2012). This may underpin the common report of executive dysfunction in remitted depression: patients show widespread deficits in attentional and executive functions compared to healthy controls, even in the absence of depressive symptomatology (Paelecke-Habermann et al., 2005; Rock et al., 2014). Directly targeting DLPFC abnormalities that underlie executive dysfunction could therefore improve clinical outcomes over and above current treatment options.

Noninvasive brain stimulation provides a possible means to target such persistent abnormalities. Both rTMS and tDCS of the DLPFC have been shown to have local and distal effects on neural activation - in the targeted DLPFC, but also in other regions including the cingulate cortex (Cho and Strafella, 2009; Stagg et al., 2013). Several previous trials have shown that DLPFC tDCS has a moderately strong antidepressant effect, comparable to that of CBT or antidepressant medication (Boggio et al., 2008; Brunoni et al., 2013; Fregni et al., 2006a; Loo et al., 2012; Nord and Roiser, 2015; Shiozawa et al., 2014). Indeed, an RCT has also tested DLPFC tDCS as an augmentative strategy to a typical course of the antidepressant medication sertraline, finding that the combined treatment showed significantly greater efficacy than either medication or tDCS alone (Brunoni et al., 2013).

In the case of CBT, the argument for a putative augmentative effect of tDCS is even stronger. A wealth of studies claim that DLPFC tDCS can cognitively 'enhance' many difficult tasks, including planning (Dockery et al., 2009), insight (Metuki et al., 2012), and selective attention (Gladwin et al., 2012). Among these, a number of studies suggest a consistent improvement in cognitive control during or after tDCS delivery, in particular working memory, in both healthy controls (Fregni et al., 2005; Lally et al., 2013), and depressed patients (Oliveira et al., 2013). Recent work even suggests that tDCS may induce a sustained improvement on working memory, lasting several months (Au et al., 2016; Ruf et al., 2017). That said, it must be acknowledged that the effect of tDCS on working memory varies widely between studies (Horvath et al., 2015); even within the same study, tDCS has been reported to improve one measure of working memory but not another (Andrews et al., 2011). In particular, while some work indicates a cumulative positive effect of tDCS on working memory in depressed patients (Fregni et al., 2006b; Richmond et al., 2014), others have failed to show any

cumulative effect on cognition with multiple stimulation sessions (Lally et al., 2013; Martin et al., 2013; Talsma et al., 2017). Indeed, one meta-analysis reported a non-significant effect of tDCS across multiple types of working memory paradigms (Horvath et al., 2015).

If DLPFC tDCS does improve difficult cognitive tasks, then based on the cognitive neuropsychological model we would predict that it might improve patients' ability to benefit from CBT, which entails many different types of difficult cognitive processing, including planning, working memory, and counterfactual thinking. This notion is strengthened by studies showing that tDCS improves cognitive control in healthy controls (Vanderhasselt et al., 2013) and depressed patients (Wolkenstein and Plewnia, 2013), and preliminary evidence suggesting that tDCS successfully enhances the antidepressant effect of other forms of psychological therapy, cognitive control training (Brunoni et al., 2014a; Segrave et al., 2014) and psychodynamic psychotherapy (Nejati et al., 2017) (note that in the latter study, only four patients received tDCS and therapy, and there was no sham tDCS condition). However, tDCS has not yet been tested in combination with CBT, the most widely-used psychological therapy for depression.

This chapter reports on the first randomized controlled trial of tDCS to augment CBT in depression. This was a mechanistic, proof-of-principle trial to establish (1) whether tDCS augments the ability of CBT to treat depression over and above our placebo condition, sham tDCS; (2) whether any clinical effects of tDCS were driven by changes in working memory, measured using the n-back task; and (3) the neural changes resulting from CBT and tDCS (compared to CBT and sham stimulation). We also investigated predictors of treatment response in this trial, which will be

presented in Chapter 6: in this chapter, we focus solely on the clinical, cognitive, and neural effects resulting from combining tDCS and CBT.

5.3 Methods

5.3.1 Participants

We recruited 39 patients who met criteria for a current major depressive disorder episode through the Camden and Islington NHS Foundation Trust Improving Access to Psychological Therapies (IAPT) Service. Potential patients were initially identified by a member of the IAPT clinical team if they met the following criteria: willingness to take part in research, a patient health questionnaire (PHQ-9) score of 15 or above, indicating moderate depression; not currently taking antidepressant medication; and internal NHS criteria for one-on-one cognitive behavioural therapy for depression ("Step 3" therapy).

To determine the latter, a clinician at the NHS centre made an in-person assessment of severity and risk. Patients with less severe symptoms were assigned to low-intensity psychotherapy sessions, typically with a more junior (non-doctoral level) clinician ("Step 2" therapy) while patients with severe personality disorders were assigned to a clinician specializing in more complex cases ("Step 4" therapy). At the clinic, an assessment was also made about the primary complaint: in many cases, a patient met the eligibility criteria for the trial, but the assessing therapist believed the focus of the therapy was better placed on another presenting issue, for example, bulimia nervosa or body dysmorphic disorder. Additionally, some patients were given more than one psychotherapeutic option by the assessing clinician, leading to non-eligibility for the trial in cases where the patient elected to receive a different type of

therapy (e.g., couples' therapy; dialectical behavioural therapy). Only patients meeting criteria for moderate depression where the clinic assigned "Step 3" CBT for depression were included in the trial.

After this initial assessment of eligibility, all eligible and interested patients (N=71) were contacted and screened in person by the lead researcher (C.N.). At this session, patients practiced the working memory task (the n-back task), completed baseline questionnaires and depression scales, and those who were native English speakers or who had been educated in English during high-school (N=23) were administered the WTAR, which we used to estimate FSIQ. All patients were screened for current or past psychiatric disorders using the MINI, version 5.0.0 (Sheehan et al., 1998). We screened for use of any psychotropic medication, past or present substance or alcohol dependence (save for a remote history of abuse or dependence restricted to a prior major depressive episode), illegal drug use within the past month, neurological illness, major health conditions likely to affect cognitive performance, and prior or present manic or psychotic symptoms (with the exception of psychotic depression). Additionally, we excluded patients who did not meet MRI safety criteria, which included presence of any irremovable ferromagnetic metal in or on the body, and medical conditions that might increase the risk of the MRI scan: pregnancy, severe claustrophobia, back pain, or severe asthma.

Following the screening session, eligible patients were recruited to the study, after which they were placed on the IAPT waiting list for one-on-one CBT. Between one week and six months after the initial assessment (mean=58.6 days; SD=40.2 days), patients received their first MRI scan and began their course of CBT. All MRI scans were collected between 1 and 6 days before starting therapy. In the case of more

than one month elapsing between initial assessment and the beginning of CBT, our primary depression measure (the HAM-D) was repeated.

The 39 patients who were not excluded before their first therapy session were randomly allocated to active (N=20) or sham (N=19) tDCS conditions. Patients, trial investigators, and therapists were all blind to tDCS condition for the duration of the trial. Following randomization, six patients discontinued therapy and/or tDCS at some point during the subsequent seven sessions. Thirty-three completed a short course of CBT (19 assigned to active stimulation, and 14 to sham; the dropout rates were not significantly different from one another (p=0.091)). For 31 patients, this included 8 sessions of CBT; 2 patients received only 7 sessions of CBT. See Figure 5.1 for Consort diagram.

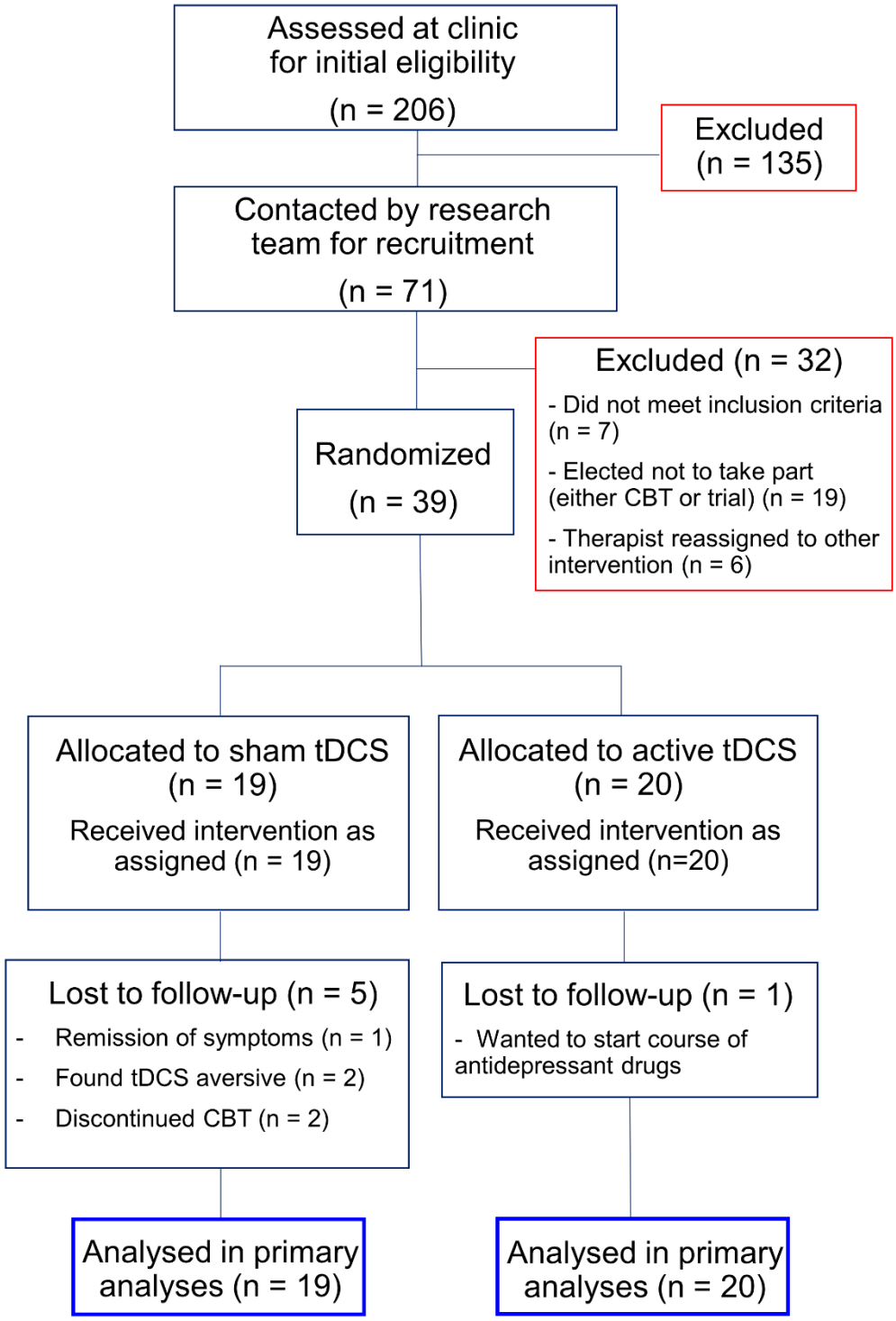

Figure 5.1 Consort diagram describing recruitment, randomization, and attrition in the clinical trial.

5.3.2 Study procedures

5.3.2.1 Protocol

The study protocol was registered on *clinicaltrials.gov* (Identifier: NCT01875419). The registered primary outcome measure was clinical response according to interview-rated mood score, measured using the 17-item HAM-D. All HAM-D interviews were conducted by the same researcher (C.N.). A minority of stimulation sessions were conducted by other trial researchers, who were trained by C.N. on stimulation delivery.

The structure of the trial is depicted in Figure 5.2. At the initial screening and recruitment session, baseline depression (HAM-D and BDI), anxiety (BAI), and anhedonia (SHAPS) measures were collected. Following the wait time for therapy, patients underwent an MRI scan shortly (0-6 days) before starting CBT. The MRI scan involved a short anatomical scan, two functional scans (during the n-back working memory task, and the emotional processing task, respectively), and two fieldmap scans (one per functional scan), and lasted 30 minutes in total. Patients were then randomized to active or sham conditions. For all patients who did not drop out during the intervention (N=33), a second MRI scan was scheduled shortly (0-6 days) after their final CBT session. The second MRI scan was identical to the first, and was followed by a final HAM-D interview.

5.3.2.2 Stimulation procedure

The tDCS sessions took place at the clinic directly preceding each CBT session. At each tDCS session (up to 8, but a minimum of 1, including dropouts), patients completed the BDI, BAI, and SHAPS, and performed the n-back working memory

task while receiving tDCS. At each session, patients also completed a questionnaire measuring tDCS side-effects

We delivered 1 mA of constant current for 20 minutes using a neuroConn DC-stimulator (neuroConn, Ilmenau, Germany) with double-blind sham stimulation control. The anodal electrode was placed near location F9 on the international 10-20 EEG system (using an EEG cap for placement), secured in place with an elasticated head strap, and the cathodal electrode was placed on the ipsilateral deltoid muscle. Both electrodes were 30cm^2, rubber, and placed inside electrode sponges that had been briefly soaked in saline to conduct the current. Sham stimulation involved 30 seconds of direct current followed by 1,170 seconds without stimulation (i.e., the rest of the 20 minutes). The initial 30 seconds of stimulation produces a similar sensation to active tDCS, resulting in effective blinding. Random assignment of stimulation condition was performed using custom-written MATLAB code by a researcher not involved in the trial. Researchers involved in the trial were given a list of five-digit codes to input to the stimulator, half of which corresponded to active stimulation and half to sham.

5.3.2.3 Therapy procedure

For patients in both arms of the trial, therapy sessions were delivered a minimum of 6 days apart. We attempted to decrease potential between-therapist variance by working with a selected team of nine therapists, all senior doctoral-level clinical psychologists in the local IAPT service. Additionally, to ensure therapists' techniques were relatively comparable, we ran a day-long training course for all trial therapists before recruitment began, delivered by a world expert in CBT for depression (S. Hollon). Briefly, CBT relies on the assumption that depressive beliefs and thoughts

are learned, and that actively changing related cognitions and behaviours will modify depressive symptoms (Beck, 1979; Beck et al., 1979). The psychological intervention consists of therapists training patients to systematically document information, including habits, plans, and emotions to offset negative biases in cognition, and to challenge negative beliefs (Beck et al., 1979; Hollon et al., 2006b).

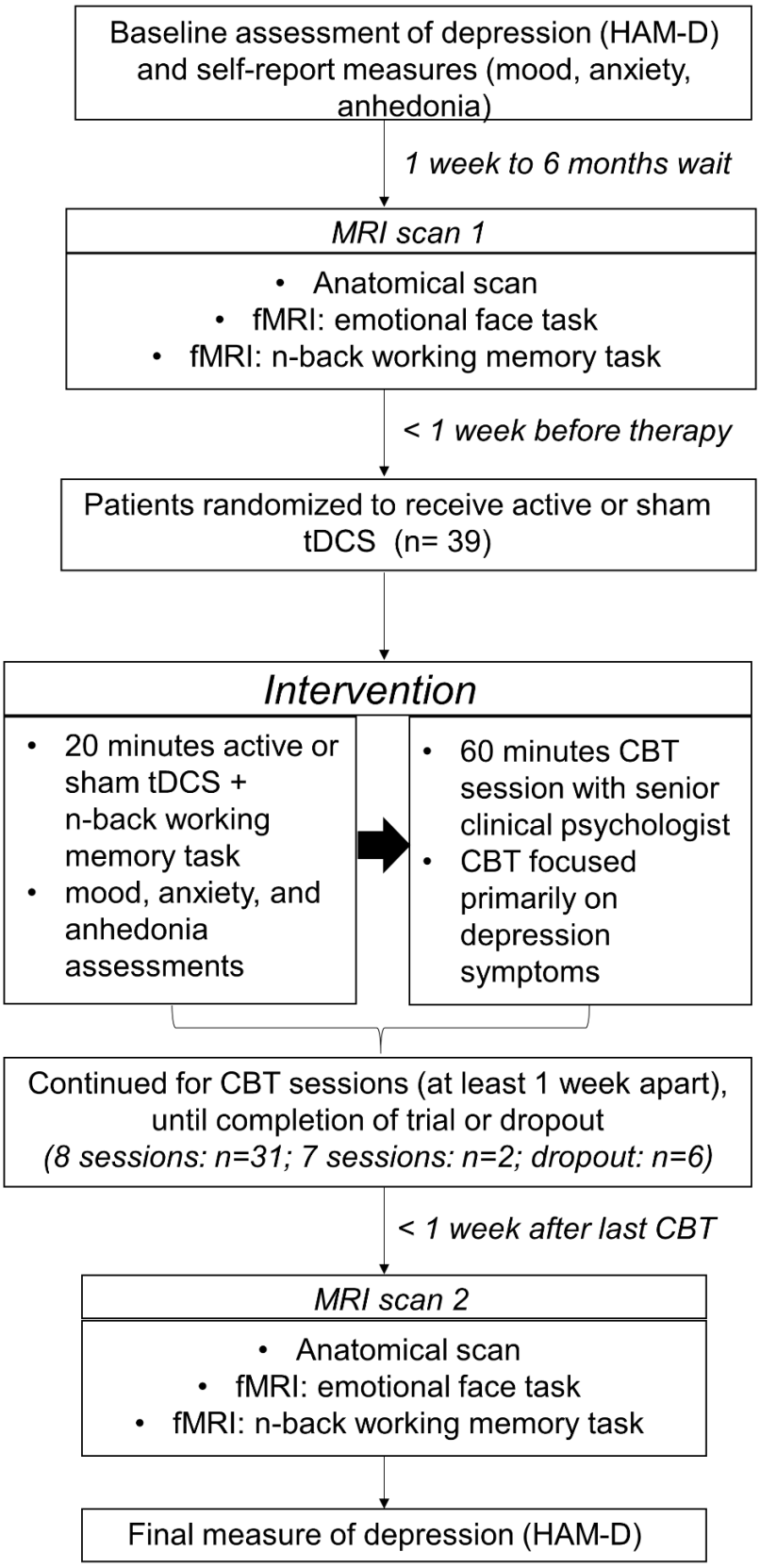

Figure 5.2 Trial protocol and typical timeline of trial patients. HAM-D = Hamilton Rating Scale for Depression; tDCS = transcranial direct current stimulation; CBT = cognitive behavioural therapy; (f)MRI = functional magnetic resonance imaging.

5.3.2.4 MRI

We used the same two tasks employed in Chapter 4: the n-back working memory task, and the emotion processing task (see Chapter 4 for full task details). MRI scans involved the acquisition of one anatomical scan, and two functional scans (with echo planar imaging, EPI) and fieldmaps (one for each task). Subjects used an MRI-compatible button box to make responses during the tasks. All acquisition parameters were identical to those reported in Chapter 4.

5.3.2.5 Side effect data

Following each tDCS session, we conducted the tDCS Adverse Events Questionnaire (Brunoni et al., 2011). We collected this data on 269 sessions in total; for four participants, side effect data was not collected on one session due to time constraints, so each only contributed seven sessions of data.

5.3.2.6 Verification of blinding

At the end of each stimulation session, participants guessed their blinding condition ("placebo" or "active" stimulation). We recorded the most frequent guess for each participant, and compared it with the actual stimulation group to verify blinding.

5.3.3 Analysis

Weekly scores were calculated for the BDI, BAI, and SHAPS, and weekly performance on the n-back task was measured as d-prime on the n-back task, which incorporates both hits and false alarms in the 3-back condition (see Chapter 2 for detailed description of calculation).

Our primary outcome measure was response rate according to the HAM-D, defined as a reduction of at least 50% from the baseline score; we also report remission rate, defined as a score of 7 or below. We analysed our primary outcome using an intent-to-treat analysis (using last observation carried forward), since we could not assume that trial attrition occurred completely at random. As a sensitivity analysis we also report the results using a per-protocol approach (i.e., including only the 33 patients who completed the trial). As a secondary measure, we also analyse HAM-D treated as a continuous measure using both intent-to-treat and per-protocol approaches.

We also analysed secondary measures of mood (BDI), anxiety (BAI), and anhedonia, as well as working memory (n-back performance) using a linear mixed model (SPSS, Version 22, IBM Corp., New York: 2012) which accounts for missing data by estimating the trajectory of change for the subjects who did provide data. These variables were collected at every stimulation session. For these variables the model included effects of time (i.e., for the majority of patients, 8 sessions), stimulation group (active/sham), and the interaction between the two as fixed effects, and participant as a random effect. We employed a heterogenous first order autoregressive covariance structure, which does not assume homogenous variance between conditions, but which is useful for data where each measurement is most closely correlated with its proximal measurements, with correlations decreasing with distance.

For the fMRI data, we could only reasonably examine the effects of the intervention on scans in the patients who completed the trial (i.e., those for whom we had a second scan); thus, all fMRI analyses are based on the per-protocol sample (N=33). We initially analysed fMRI results using a similar approach to Chapter 4. Our primary

analysis extracted average activation across our ROIs of interest: for the n-back task, the bilateral DLPFC (using coordinates from a previous meta-analysis of the n-back task in depression (Wang et al., 2015)); for the emotion processing faces task, the amygdalae (anatomical ROI: WFU Pick Atlas, version 3.0.5) and the subgenual anterior cingulate cortex (using a custom-made ventral anterior cingulate ROI, which comprised Brodmann Area 25 and the ventral portion of Brodmann Area 24). However, unlike in Chapter 4, we also examined a fourth ROI in the emotion processing task: the region of stimulation, i.e. left DLPFC.

We additionally conducted a flexible factorial analysis across the whole brain in a voxel-wise fashion in SPM data to reveal the effect of therapy and stimulation condition in regions not hypothesized *a priori* to differ between active and sham tDCS conditions. These analyses were submitted to whole-brain correction for multiple comparisons, controlling the family-wise error rate (cluster-forming threshold of $p<0.001$ (uncorrected)).

5.3.4 Power calculation

This trial was a preliminary study to assess feasibility and safety of augmenting CBT with tDCS, and to explore possible mechanistic measures associated with response to treatment. Therefore, a power analysis was not carried out based on the primary outcome measure, response rate according to the HAM-D. However, a previous report of tDCS in depression reported a large effect size (d~0.9) for our secondary outcome, HAM-D treated as a continuous measure (Fregni et al., 2006a); with this effect size, at $\alpha = 0.05$, we required a sample size of N=20 per group to achieve 80% power.

5.4 Results

5.4.1 Clinical and demographic data

Independent-samples t-tests with group as the between-subjects factor revealed no differences between the study arms in terms of age, age of onset of depression, FSIQ, number of episodes, or any baseline clinical measure (HAM-D, BDI, BAI, or SHAPS scores, all $p>0.1$) (see Table 5.1). Pearson Chi-Square tests also showed no differences between the study arms in terms of sex, family history of depression, or previous history of hospitalization, suicide, antidepressant medication, or psychotherapy (all $p>0.09$).

	active tDCS mean (SD)	sham tDCS mean (SD)	group difference
N	20	19	n/a
% F	45.00	57.89	$X^2_{(1)}$=0.65, p=0.527
Age	35.60 (12.91)	31.05 (8.17)	t(37)=1.32, p=0.196
FSIQ	110.10 (7.49)	105.15 (7.54)	t(21)=1.56, p=0.133
Baseline HAM-D	21.95 (3.20)	21.05 (3.27)	t(37)=0.87, p=0.393
Baseline BDI	25.70 (8.01)	27.79 (5.34)	t(37)=0.34, p=0.738
Baseline SHAPS	19.85 (7.25)	18.05 (7.25)	t(37)=0.80, p=0.429
Baseline BAI	25.70 (13.57)	25.47 (12.06)	t(37)=0.06, p=0.956
Age of onset	22.80 (10.09)	18.37 (8.23)	t(37)=1.50, p=0.143
No. episodes	2.50 (1.67)	3.05 (1.58)	t(37)=1.06, p=0.296
% hospitalized	15.00	15.79	$X^2_{(1)}$=0.01, p=1.00
% suicide attempt	30.00	21.05	$X^2_{(1)}$=0.41, p=0.716
% past ADM	55.00	42.10	$X^2_{(1)}$=0.65, p=0.527
% past PT	50.00	78.9	$X^2_{(1)}$=3.55, p=0.096

Table 5.1 Participant characteristics by stimulation condition. SD = standard deviation; F = female; FSIQ = Full Scale Intelligence Quotient (calculated from Weschler Test of Adult Reading); HAM-D = Hamilton Rating Scale for Depression; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory; SHAPS = Snaith-Hamilton Pleasure Scale; No. = number; % past ADM = percent of patients with any previous history antidepressant medication use (no patients were currently-medicated: see Methods); % past PT = percent of patients with a history of psychological therapy.

5.4.2 Side effect analysis

All patients reported at least one side effect on at least one stimulation session. The most common symptom reported was tingling, reported on 80% of active and 73% of sham stimulation sessions (no significant difference between stimulation conditions, X^2=1.60, p=0.206). Headache was reported significantly more in the sham condition (X^2=11.26, p=0.001), as was burning sensation (X^2=5.10, p=0.024), sleepiness (X^2=17.79, p<0.001), and trouble concentrating (X^2=22.26, p<0.001; note that side-effects were assessed immediately following the n-back task). Itching and skin redness were reported significantly more frequently in the active condition (X^2=16.05, p<0.001; X^2=35.28, p<0.001). Correcting for multiple comparisons (N=10 side-

effects), there was no longer a significant difference in burning sensation between the groups (Bonferroni-adjusted threshold: p=0.005), though the other differences remained significant. Note that the false positive rate is likely to be elevated for these analyses as observations over successive trial sessions within an individual are probably not independent from one another. See Table 5.2 for a full description of reported side effects across all tDCS sessions.

Side effects (active stimulation)	% sessions	No. instances	% mild	% moderate	% severe	% "unrelated" to stimulation	% “remotely” related	% “possibly” related	% “probably” related	% “definitely” related
Headache	12.1	18	61.1	16.7	22.2	33.3	11.1	22.2	0.0	0.0
Neck pain	6.7	10	90.0	0.0	10.0	50.0	10.0	10.0	20.0	0.0
Scalp pain	18.8	28	60.7	35.7	3.6	17.9	0.0	28.6	39.3	0.0
Tingling	79.9	119	63.0	27.7	9.2	9.2	16.0	17.6	53.8	1.7
Itching	54.4	81	50.6	32.1	17.3	8.6	17.3	17.3	53.1	1.2
Burning	25.5	38	65.8	23.7	10.5	10.5	7.9	18.4	65.8	2.6
Skin redness	28.9	43	69.8	23.3	7.0	14.0	18.6	2.3	62.8	0.0
Sleepiness	34.2	51	41.2	33.3	25.5	11.8	35.3	31.4	9.8	3.9
Trouble concentrating	46.6	68	38.2	38.2	23.5	13.2	38.2	16.2	8.8	2.9
Mood changes	16.1	24	41.7	29.2	29.2	33.3	33.3	12.5	16.7	8.3
Side effects (sham stimulation)	% sessions	No. instances	% Mild	% moderate	% severe	% "unrelated" to stimulation	% “remotely” related	% “possibly” related	% “probably” related	% “definitely” related
Headache	28.3	34	73.5	14.7	11.8	32.4	32.4	14.7	0.0	0.0
Neck pain	12.5	15	66.7	33.3	0.0	33.3	20.0	13.3	0.0	0.0
Scalp pain	19.2	23	56.5	43.5	0.0	8.7	13.0	39.1	39.1	0.0
Tingling	73.3	88	54.5	43.2	2.3	1.1	15.9	45.5	31.8	5.7
Itching	30.0	36	58.3	27.8	13.9	5.6	27.8	16.7	41.7	5.6
Burning	38.3	46	58.7	32.6	8.7	4.3	8.7	47.8	30.4	4.3
Skin redness	1.7	2	50.0	50.0	0.0	100.0	0.0	0.0	0.0	0.0
Sleepiness	60.0	72	41.7	31.9	26.4	27.8	23.6	26.4	8.3	1.4
Trouble concentrating	74.2	89	48.3	40.4	11.2	31.5	27.0	14.6	4.5	0.0
Mood changes	13.3	16	81.3	12.5	6.3	25.0	56.3	6.3	0.0	0.0

Table 5.2 Side effects in active and sham groups. No.=number.

5.4.3 Assessment of blinding

We assessed the blinding by testing whether patients guessed their condition better than chance: patients correctly guessed their condition in only 38.5% of cases (not significantly different from chance: p=0.337). Across both groups there was a bias for patients to believe they were in the active condition: most (69.2%) guessed they were on active stimulation. In the sham group, 78.9% guessed they were receiving active stimulation (21.1% guessed sham); in the active group, 60% guessed they were receiving active stimulation (40% guessed sham); there was no significant difference in the proportion of active and sham guesses between the groups (X^2=1.64, p=0.301). This suggests that, despite some differences in reported side-effects (described above), the blinding procedure was effective.

5.4.4 Primary outcome: clinical response

Our primary outcome measure was clinical response, defined as a reduction of 50% or more in the HAM-D. We also examined clinical remission, defined as a total score of 7 or less on the HAM-D. For these measures only, we report one-tailed tests due to the directionality of our hypothesis (i.e., that active tDCS would result in a greater proportion of clinical response and remission than sham). Using an intention-to-treat (ITT) analysis (last observation carried forward, N=39), more patients responded (active: 50%; sham: 31.6%; odds ratio: 2.16, 95%CI=0.59—7.99) and remitted (active: 30%; sham: 10.5%; odds ratio: 3.65, 95%CI=0.63—20.96) following CBT with active than with sham tDCS (Figure 5.3A). However, these differences did not achieve statistical significance (response: X^2=1.37, p=0.12 (one-tailed); remission: X^2=2.27, p=0.066 (one-tailed)). The results were similar when analysing the per-protocol sample (i.e., patients who completed the trial), with differences in the

direction for both response (active: 52.6%; sham: 42.9%; odds ratio: 1.48; X^2=1.313, p=0.420 (one-tailed)) and remission (active: 31.6%; sham: 14.3%; odds ratio: 2.76; X^2=0.308, p=0.234 (one-tailed)).

5.4.5 Secondary outcome: HAM-D score change over time

We also examined HAM-D score continuously using repeated-measures ANOVA, with a within-subjects factor of time (pre- and post-therapy) and a between-subjects factor of stimulation condition. Both pre- and post-therapy HAM-D scores conformed to assumptions of normality (Kolmogorov-Smirnov test, both p>0.08).

There were no baseline differences in HAM-D between the active and sham groups, either in the full sample (ITT analysis: t(37)=0.845, p=0.393) or only those treated per-protocol (t(31)=0.410, p=0.685).

In the ITT analysis using LOCF, depression scores reduced significantly from pre- to post-intervention (F(1,37)=56.09, p<0.001, η_p^2=0.603), but there was no interaction with stimulation condition (F(1,37)=1.50, p=0.228). In the sham group, HAM-D decreased from a mean of 21.05 (SD = 3.27) to 14.37 (SD = 5.81), a mean difference of 6.68 points (SD = 6.49). In the active group, HAM-D decreased from a mean of 21.95 (SD = 3.20) to 12.65 (SD = 6.91), a mean difference of 9.30 points (SD = 6.82). There was no main effect of stimulation condition (F(1,37)=0.112, p=0.739) (Figure 5.3B).

The per-protocol analysis yielded similar results: HAM-D scores reduced significantly from pre- to post-intervention (F(1,31)=64.07, p<0.001, η_p^2=0.674), but there was no interaction with stimulation condition (F(1,31)=0.02, p=0.881). Again, there was no

main effect of stimulation condition ($F(1,31)=0.048$, $p=0.828$). Here, the active group decreased from a HAM-D score of 21.89 (SD = 3.28) to 12.42 (SD = 7.05), a mean difference of 9.42 (SD = 6.99) points; the sham group decreased from a HAM-D of 21.43 (SD = 3.16) to 12.36 (SD = 5.09), a mean difference of 9.07 (SD = 5.92) points.

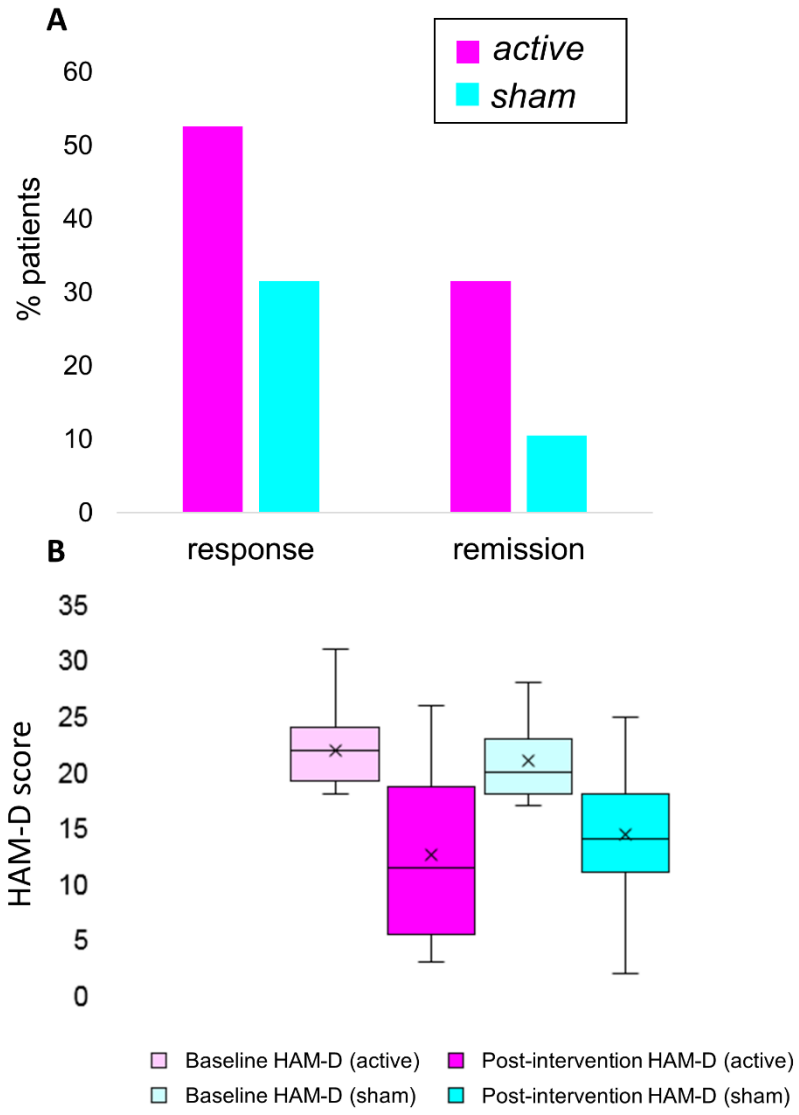

Figure 5.3 Clinical outcomes. Percent of patients meeting criteria for clinical response and remission (A) and patients' overall change in depression score (B), both measured using the Hamilton Depression Rating Scale (HAM-D) (ITT analysis). The effect of stimulation was non-significant for both (p>0.05). In (B), horizontal lines represent the median; x represents the mean; lower error bars represent the distance between the first quartile and the minimum score, while upper error bars represent the distance between the third quartile and maximum score.

5.4.6 Secondary outcome: BDI

There were no significant differences between the active and sham groups' baseline (pre-intervention) BDI scores, either including the whole sample (ITT analysis: $t(37)=0.337$, $p=0.738$), or only the sample who completed the trial (per-protocol analysis: $t(31)=0.920$, $p=0.364$).

In the ITT analysis using a mixed linear model, BDI scores decreased significantly from pre- to post-intervention (F(7, 108.80)=2.99, p=0.007), but this did not interact with stimulation condition (F(7, 108.80)=0.274, p=0.963), nor was there a main effect of stimulation condition (F(1, 35.82)=0.081, p=0.777). Data are presented in Figure 5.4A.

5.4.7 Secondary outcome: BAI

There were no significant differences between active and sham groups' baseline anxiety scores, as measured with the BAI, either including the whole sample (ITT analysis: t(37)=0.055, p=0.956), or only the sample who completed the trial (per-protocol analysis: t(31)=0.226, p=0.823).

In the ITT analysis using a mixed linear model, BAI scores also improved significantly with time (F(7, 139.56)=2.16, p=0.042). There was no effect of stimulation condition (F(1, 40.10)=0.332, p=0.568), nor an interaction between time and stimulation condition (F(7, 139.56)=0.871, p=0.531). Data are presented in Figure 5.4B.

5.4.8 Secondary outcome: SHAPS

There were no significant differences between active and sham groups' baseline anhedonia scores, as measured with the SHAPS, either including the whole sample (ITT analysis: t(37)=0.8, p=0.429), or only the sample who completed the trial (per-protocol analysis: t(31)=0.049, p=0.961).

In the ITT analysis using a mixed linear model, SHAPS scores did not improve significantly with time (F(7,131.56)=0.685, p=0.684), nor was there an effect of

stimulation condition (F(1, 39.52)=0.343, p=0.561), or an interaction between the two (F(7, 131.56)=0.561, p=0.794). Data are presented in Figure 5.4C.

5.4.9 Working memory measure: n-back task

Surprisingly, in the ITT analysis using a mixed linear model, the improvement over time in n-back performance did not reach significance (F(7,149.96)=1.99, p=0.060), and there was no effect of stimulation condition (F(1,40.57)=0.340, p=0.563) or interaction between the two (F(7,149.96)=0.421, p=0.888). Data are presented in Figure 5.4D.

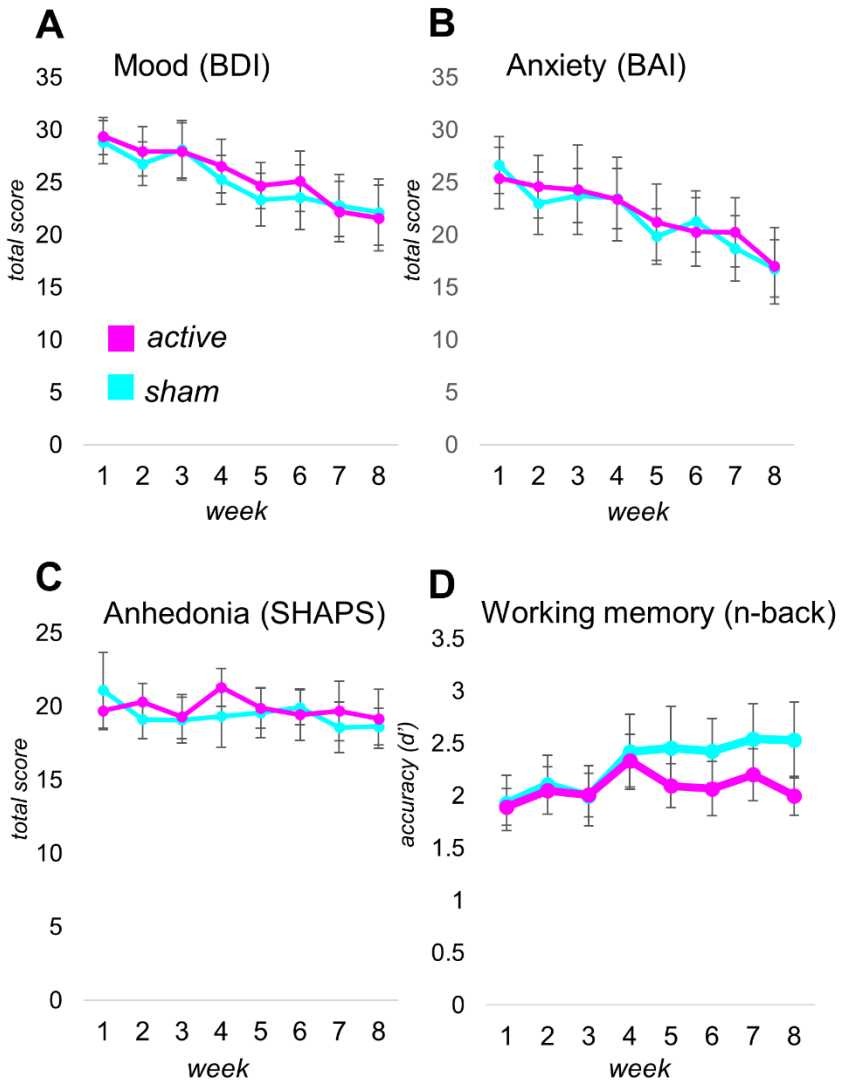

Figure 5.4 Effect of intervention on clinical and cognitive measures. Weekly mood (A), anxiety (B), and anhedonia (C) self-report scores ratings, and performance on the working memory (n-back) task (D), for each stimulation condition. Error bars represent standard error of the mean. BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory; SHAPS = Snaith-Hamilton Pleasure Scale.

5.4.10 Secondary outcome: effect of tDCS on neural activation

For consistency with the fMRI analysis, behavioural data collected inside the MRI scanner were analysed using a per-protocol approach.

Behavioural data on the n-back task (d-prime) acquired inside the scanner met assumptions of normality on both sessions (Kolmogorov-Smirnov test, both p=0.2), but behavioural data on the emotion processing task (% correct gender classification) did not, either pre- or post-intervention (both p<0.001).

In a repeated-measures ANOVA with a within-subjects factor time (pre- or post-intervention) and a between-subjects factor of stimulation condition, n-back performance improved significantly over time ($F(1,31)=28.46$, $p<0.001$). There was no main effect of group ($F(1,31)=1.01$, $p=0.323$). Surprisingly, performance improved more in the sham than the active group (significant group-by-time interaction: ($F(1,31)=6.17$, $p=0.019$). In the sham group, baseline d' was 1.41 (SD = 0.82), rising to 2.76 (SD = 1.37), a mean improvement of 1.35 (SD = 1.27); in the active stimulation group, baseline d' was 1.55 (SD = 0.72), rising to 2.04 (SD = 0.89), a mean improvement of 0.49 (SD = 0.70).

There was no effect of group on performance in the emotion processing task: a non-parametric Mann-Whitney U test revealed no effect of group on the difference between post-intervention and pre-intervention accuracy at gender identification (examined separately, there were also no group differences before ($p=0.439$) or after ($p=0.483$) the intervention: in the sham group, baseline accuracy was 98.1% (SD = 0.02), and post-intervention accuracy was 97.5% (SD = 0.03), a mean difference of -0.01 (SD = 0.02); in the active group, baseline accuracy was 96.5% (SD = 0.08), and post-intervention accuracy was 95.0% (SD = 0.08), a mean difference of -0.02 (SD = 0.07).

For the fMRI analysis, for each task, we constructed ANOVAs examining the effects of stimulation group, time and their interaction on activation (averaged across the ROI): in the case of the n-back task this was in the bilateral DLPFC; in the case of the emotional faces task this was in the sgACC, amygdalae, and left DLPFC.

To identify effects of stimulation and time outside of our hypothesized ROIs, we conducted a flexible factorial model in SPM, including the effects of group (active or sham), time (pre- or post-intervention) and their interaction. For this exploratory analysis, we report all cluster- or voxel-level FWE significant (p<0.05) activations at the whole-brain level (results reported in tables: initial cluster forming threshold: p<0.001 (uncorrected), minimum cluster size k=4). In cases where we found no significant whole-brain activation in our hypothesized ROIs, we also present significant small volume-corrected (SVC) results.

5.4.10.1 Effect of tDCS and time on DLPFC activation during working memory (average over ROI)

To examine the effect of stimulation on DLPFC activation (3- vs 1-back contrast), we conducted a repeated-measures ANOVA with within-subjects factors of laterality (left, right) and time (pre-, post-intervention) and a between-subjects factor of stimulation (active or sham). With the exception of right DLPFC activation on the post-intervention scan, data met the assumption of normality. For the right DLPFC, we conducted a nonparametric independent samples Kruskal-Wallis test, testing the effect of group on the post-intervention scan, which confirmed the results of the ANOVA (p>0.1).

Activation was stronger in the left than the right DLPFC (main effect of laterality: $F(1,31)=5.00$, $p=0.033$, $\eta_p^2=0.139$) and increased after the intervention (main effect of time: $F(1,31)=20.95$, $p<0.001$, $\eta_p^2=0.403$) (see Figure 5.5), but the interaction was non-significant ($F(1,31)=0.363$, $p=0.551$). There was also no interaction between laterality and stimulation condition ($F(1,31)=2.84$, $p=0.102$), between time and stimulation condition ($F(1,31)=0.095$, $p=0.760$), or between laterality, time, and

stimulation condition ($F(1,31)=1.330$, $p=0.258$). The main effect of stimulation condition was non-significant ($F(1,31)=1.29$, $p=0.266$).

At baseline patients showed significantly lower bilateral DLPFC activation than matched healthy controls (as reported in Chapter 4; this was also the case in the sample of 33 patients in the per-protocol analysis: significant main effect of group: $F(1,61)=8.24$, $p=0.006$, $\eta_p^2=0.119$). However, a similar analysis did not reveal any significant difference in post-intervention DLPFC activation between patients and healthy controls (main effect of group: $F(1,61)=0.191$, $p=0.664$). There was no association between the increase in DLPFC activation and improvement on the n-back task ($r(33)=0.064$, $p=0.725$).

5.4.10.2 Whole-brain effects of tDCS and time on working memory

From the flexible factorial analysis in SPM, an *F*-contrast for the main effect of time (pre- versus post-intervention) revealed significantly increased activation from pre- to post-intervention in the bilateral parietal cortices and bilateral DLPFC, and significantly decreased activation in the medial prefrontal cortex (mPFC), extending into the perigenual ACC (all $p<0.001$, cluster-level FWE-corrected) (Table 5.3).

A contrast for the main effect of stimulation condition revealed that patients receiving active stimulation showed greater activation in the right posterior parietal cortex (rPPC) (k=33) compared to sham (see Table 5.3); this was significant with whole-brain voxel-level correction (voxel-level corrected $p=0.02$; cluster-level corrected $p=0.153$). Although an *F*-contrast for the interaction between group and time found no whole-brain significant activation (all $p<0.9$, cluster-level), the group effect in the rPPC did not seem to be driven by baseline differences between the groups (see

Figure 5.5E). Instead, rPPC activation increased numerically over time in the active stimulation condition but decreased numerically in the sham condition (see Figure 5.5F). See Table 5.3 for all activation data (cluster-forming threshold: $p<0.001$, uncorrected; minimum cluster size k=4).

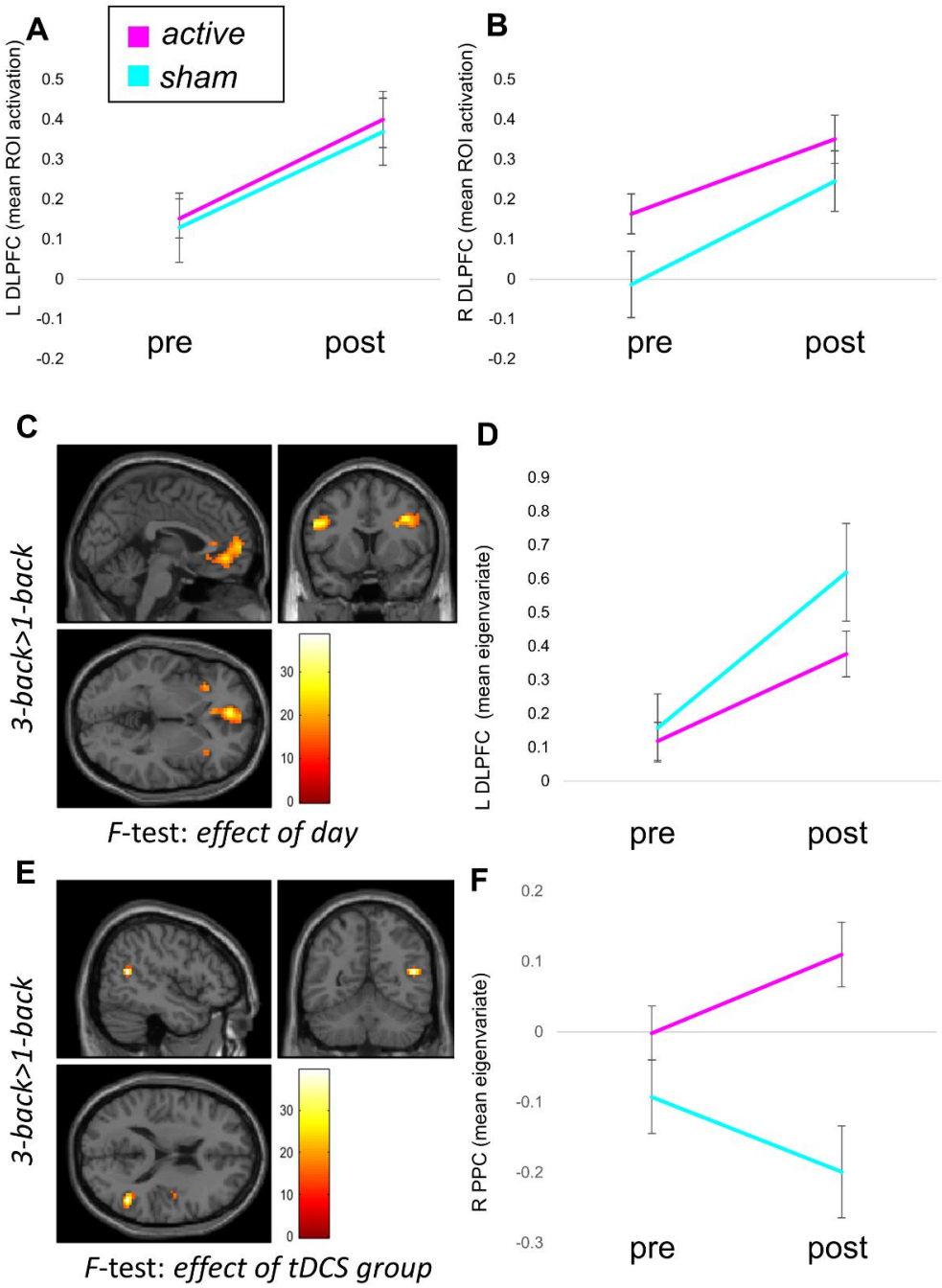

Figure 5.5. Effect of intervention on fMRI ROI activation (working memory). Activation in left dorsolateral prefrontal cortex (L DLPFC) predefined region-of-interest (A) and right dorsolateral prefrontal cortex (R DLPFC) predefined region-of-interest (B) pre- and post-intervention, separated by active (magenta) and sham (cyan) tDCS condition. Across L&R DLPFC, activation increased after the intervention ($F(1,31)=20.95$, $p<0.001$, $\mu^2=0.403$). C: Whole brain effect of day (pre- versus post-intervention) from the flexible factorial model (contrast: 3-back > 1-back). Significant clusters in the bilateral DLPFC (increased over time – coronal section) and medial PFC/perigenual anterior cingulate cortex (decreased over time – sagittal section) are shown. D: Mean eigenvariate of left DLPFC cluster in F-test for main effect of day, pre- and post-intervention. E: Whole brain effect of group (active vs sham) from the flexible factorial model (contrast; 3-back>1-back). A significant cluster in the right posterior parietal cortex (rPPC) is shown. F: Mean eigenvariate of right PPC cluster in F-test for main effect of group, pre- and post-intervention. Overlays are thresholded at $p<0.001$, uncorrected, minimum cluster size k=4 and colour bars indicate F-values.

Effect	*p* (cluster level)	Extent (k)	*p* (voxel level)	F(1,31)	X	Y	Z	Region	Direction of effect
day	<0.001	243	0.024	38.31	-30	-61	41	L PPC	post > pre
	<0.001	326	0.040	35.64	27	-64	38	R PPC	post > pre
	<0.001	354	0.061	33.50	-6	47	-1	mPFC/pgACC	pre > post
	<0.001	196	0.062	33.48	39	8	35	R DLPFC	post > pre
	<0.001	333	0.063	33.33	-48	8	29	L DLPFC	post > pre
	0.865	7	0.489	22.77	-57	-13	-16	L lat. temporal	pre > post
	0.164	32	0.544	22.10	51	-37	53	R inferior parietal	post > pre
	0.037	54	0.651	20.89	-42	-37	50	L inferior parietal	post > pre
	0.387	20	0.690	20.46	-45	-61	-13	L fusiform	post > pre
	0.120	34	0.739	19.90	33	23	5	R insula	post > pre
	0.071	44	0.803	19.13	-6	-46	29	L posterior cingulate	pre > post
	0.600	12	0.857	18.42	33	-82	29	R angular gyrus	post > pre
	0.922	5	0.897	17.80	54	-37	14	R sup. temporal	post > pre
	0.621	13	0.935	17.09	-39	47	11	L DLPFC	post>pre
	0.922	5	0.992	14.89	-48	17	-4	L OFC	post > pre
	0.948	4	0.997	14.26	9	-49	26	R posterior cingulate	pre > post
group	0.153	33	0.020	39.40	48	-55	17	R PPC	active > sham
	0.700	11	0.187	27.92	-39	38	-13	L VLPFC	active > sham
	0.740	10	0.479	22.89	-21	53	8	L rostral PFC	sham > active
	0.922	5	0.485	22.82	-15	2	53	L sup. FG	sham > active
	0.740	10	0.533	22.24	33	-46	56	R sup. parietal	active > sham
	0.948	4	0.929	17.21	30	20	-10	R insula	active > sham
	0.948	4	0.963	16.35	42	-7	17	R prim. motor	active > sham
	0.948	4	0.990	15.09	-21	-61	32	L sup. parietal	sham > active
day*group	none								

Table 5.3 N-back task: whole-brain results. Whole-brain results of flexible factorial for n-back task (all contrasts: 3-back>1-back; cluster-forming threshold $p<0.001$, uncorrected; minimum cluster size=4) for both main effects (day, i.e. pre-invention or post-intervention; group, i.e. active or sham tDCS) and interaction effect. R=right; L=left; lat.=lateral; sup.=superior; prim.=primary; FG=frontal gyrus; PPC=posterior parietal cortex; mPFC=medial prefrontal cortex; OFC=orbitofrontal cortex; VLPFC=ventrolateral prefrontal cortex; pgACC=perigenual anterior cingulate cortex; sup.=superior; prim.=primary; DLPFC = dorsolateral prefrontal cortex.

5.4.10.3 Effect of tDCS and time on amygdala activation during emotion processing (average over ROI)

All distributions of parameter estimates for the amygdalae met the assumption of normality (Kolmogorov-Smirnov test, all $p>0.08$). We conducted a repeated-measures ANOVA, with within-subjects factors of emotion (fear, happy), laterality (left, right), and time (pre-, post-intervention), and a between-subjects factor of stimulation condition.

There was no significant effect of laterality ($F(1,31)=0.336$, $p=0.566$). The interaction between laterality and group narrowly missed significance ($F(1,31)=4.11$, $p=0.051$) and was not analysed further. Amygdala activation for the fearful>neutral contrast was significantly stronger than for the happy>neutral contrast ($F(1,31)=20.54$, $p<0.001$, $\eta_p^2=0.399$). Emotion interacted with stimulation condition ($F(1,31)=8.41$, $p=0.007$, $\eta_p^2=0.213$), such that those in the sham group showed greater amygdala activation for fearful faces, but lower amygdala activation for happy faces than those in the active group (however, post-hoc contrasts averaging across days and laterality did not show significant differences between the groups in either the fearful ($t(31)=1.110$, $p=0.276$) or happy ($t(31)=2.02$, $p=0.052$) conditions). Emotion did not interact with laterality ($F(1,31)=2.84$, $p=0.102$), and the three-way interaction between emotion, stimulation condition, and laterality narrowly missed significance ($F(1,31)=3.65$, $p=0.065$).

Although there was no main effect of time ($F(1,31)=2.00$, $p=0.168$), importantly there was a significant time-by-simulation condition interaction ($F(1,31)=5.04$, $p=0.032$, $\eta_p^2=0.140$), such that those in the sham group showed decreased amygdala activation (averaged across fear and happy) at post- relative to pre-intervention

(t(14)=2.63, p=0.021), while those in the active stimulation condition did not (t(19)=0.605, p=0.553) (see Figure 5.6A-D). However, independent-samples t-tests did not reveal significant differences between the active and sham conditions either pre- (t(31)=1.74, p=0.092) or post-intervention (t(31)=1.96, p=0.059).

There was no interaction between time and laterality (F(1,31)=0.146, p=0.705), between time and emotion (F(1,31)=0.022, p=0.882), between time, laterality, and stimulation condition (F(1,31)=0.605, p=0.443), between time, emotion, and laterality (F(1,31)=0.699, p=0.409), or between time, emotion, and stimulation condition (F(1,31)=1.86, p=0.182). There was also no four-way interaction between time, emotion, laterality, and stimulation condition (F(1,31)=2.29, p=0.140).

5.4.10.4 Effect of tDCS and time on sgACC activation during emotion processing (average over ROI)

We conducted a similar analysis (though without laterality) for the sgACC. All but one distribution of parameter estimates met the assumption of normality (Kolmogorov-Smirnov test, all p>0.2). In the one that did not (post-intervention sgACC activation in the happy>neutral faces contrast: p=0.042), we performed a nonparametric independent samples Kruskal-Wallis test, testing the effect of group on post-intervention activation, which confirmed the results of the ANOVA (p>0.3).

We found no significant main effect of stimulation condition (F(1,31)=1.61, p=0.214). There was also no main effect of emotion (F(1,31)=1.41, p=0.244), no emotion-by-stimulation condition interaction (F(1,31)=0.851, p=0.363), no main effect of time (F(1,31)=0.043, p=0.837), no time-by-stimulation condition interaction (F(1,31)=0.006, p=0.937), no time-by-emotion interaction (F(1,31)=1.28, p=0.267),

and no three-way interaction between time, emotion, and stimulation condition (F(1,31)=0.325, p=0.573) (Figure 5.6E-F).

5.4.10.5 Effect of tDCS and time on left DLPFC activation during emotion processing (average over ROI)

We conducted a similar analysis for our final ROI, the stimulated region, left DLPFC. The distributions of parameter estimates all met the assumption of normality (Kolmogorov-Smirnov test, all p>0.2).

The main effect of emotion narrowly missed significance (F(1,31)=3.91, p=0.054), and there was no emotion-by-stimulation condition interaction (F(1,31)=0.002, p=0.962), no main effect of time (F(1,31)=0.361, p=0.552), no time-by-emotion interaction (F(1,31)=0.038, p=0.846), and no three-way interaction between time, emotion, and stimulation condition (F(1,31)=0.245, p=0.624). There was no main effect of stimulation condition (F(1,31)=0.116, p=0.736).

We found a significant interaction between time and stimulation condition which mirrored the findings observed in the amygdala (F(1,31)=10.95, p=0.002, η_p^2=0.261). In patients receiving active stimulation, left DLPFC activation increased from pre-to post-intervention, though this narrowly missed significance (t(18)=2.06, p=0.055); in patients receiving sham stimulation, left DLPFC activation decreased significantly over time (t(13)=2.62, p=0.021). Collapsing across both emotions, independent-samples t-tests revealed no difference between the stimulation conditions at baseline (t(31)=1.88, p=0.07), but post-intervention there was significantly greater activation in the left DLPFC in the active stimulation group compared to the sham group (t(31)=2.08, p=0.046) (see Figure 5.6G-H).

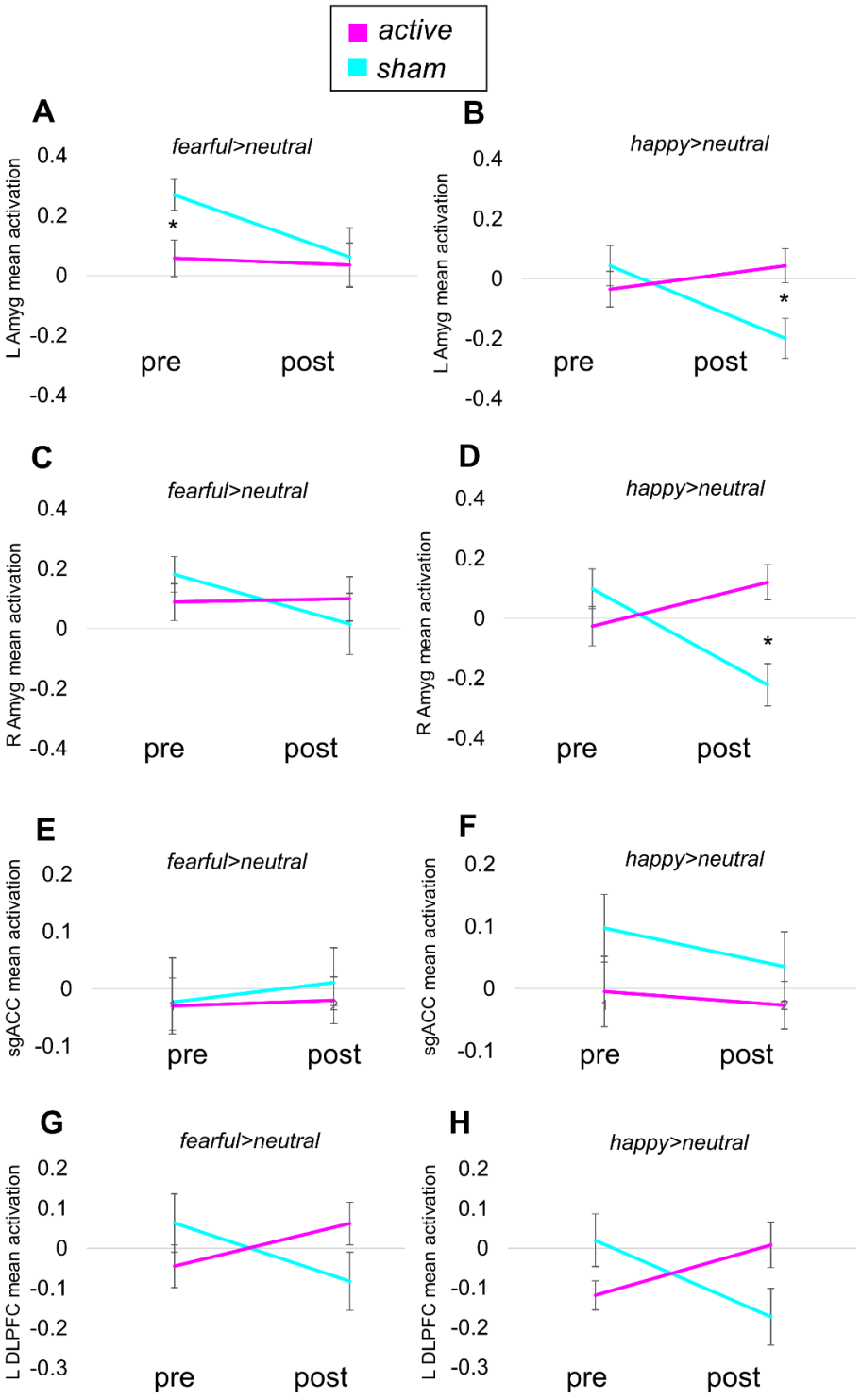

Figure 5.6. Effect of intervention on fMRI activation (emotion processing). Activation pre- and post-intervention, separated for active (magenta) and sham (cyan) tDCS conditions, for the left amygdala (L Amyg, A-B), right amygdala (R Amyg, C-D), subgenual anterior cingulate cortex (sgACC, E-F), and left dorsolateral prefrontal cortex (L DLPFC, G-H) for fearful>neutral (left column) and happy>neutral (right column) contrasts. In the amygdalae (A-D), time interacted significantly with emotion condition, ($F(1,31)=5.04$, $p=0.032$, $\eta_p^2=0.140$), such that under sham activation decreased from pre- to post-intervention. This was not the case in the sgACC (E-F). However, in the left DLPFC, we found a similar interaction in the same direction as the amygdala ($F(1,31)=10.95$, $p=0.002$, $\eta_p^2=0.261$). *=significant group difference ($p<0.05$).

5.4.10.6 Whole-brain effects of tDCS and time on emotion processing

We conducted three separate flexible factorial models, testing for the effect of tDCS group and time (before/after therapy) on (1) activation to faces, compared with fixation cross; (2) activation to happy compared to neutral faces; (3) activation to fearful compared to neutral faces.

Faces vs fixation

An *F*-contrast for the main effect of time revealed no whole-brain family-wise error significant clusters (see Table 5.4 for all clusters reaching a threshold of $p<0.001$, uncorrected; minimum cluster size k=4). An *F*-contrast for the main effect of stimulation group revealed significantly greater activation in the sham group than the active group in several extensive clusters with peaks in the bilateral posterior parietal cortices (k=2425 and k=763, both $p<0.001$, cluster-corrected for right and left, respectively) and the left angular gyrus (k=1015, $p<0.001$, cluster-corrected) (note that this collapses across both days, i.e. before and after the intervention). There were also significant clusters in the prefrontal cortices (the majority, including a left DLPFC cluster, indicating higher activation in the sham group, with the exception of a cluster in the right DLPFC ($p<0.001$, cluster-corrected), which showed greater activation in those receiving active stimulation). These group differences are hard to interpret as they were already present at baseline (see Figure 5.7). The *F*-contrast for the interaction between stimulation group and time did not identify any whole-brain significant clusters (see Table 5.4).

We also examined activation in our four ROIs (bilateral amygdala, sgACC, and left DLPFC) using small volume correction (SVC). This reiterated the group effect driven

by baseline differences found in our whole-brain analysis: there was significantly greater activation in the sham group than the active group in the left DLPFC (p<0.001, voxel-level SVC), which survived Bonferroni correction across our four ROIs (Table 5.5). No results survived correction in the other ROIs.

Fearful vs neutral

F-contrasts for the main effect of time, stimulation group, and their interaction revealed no significant effects at the whole-brain level (all p>0.3, cluster-level, FWE-corrected). There were also no significant effects of group, day, or any interactions in the four ROIs examined following SVC.

Happy vs neutral

F-contrasts for the main effects of time and stimulation condition revealed no significant effects at the whole-brain level; an *F*-contrast for the interaction between stimulation group and time also did not find any significant clusters at the whole-brain level. SVC within our four ROIs revealed a group-by-time interaction in the left DLPFC (p=0.038 SVC): from pre- to post intervention, patients receiving sham stimulation showed decreased left DLPFC activation over time, while those receiving active showed increased left DLPFC activation over time (though this did not survive correction for four ROIs (see Table 5.5)).

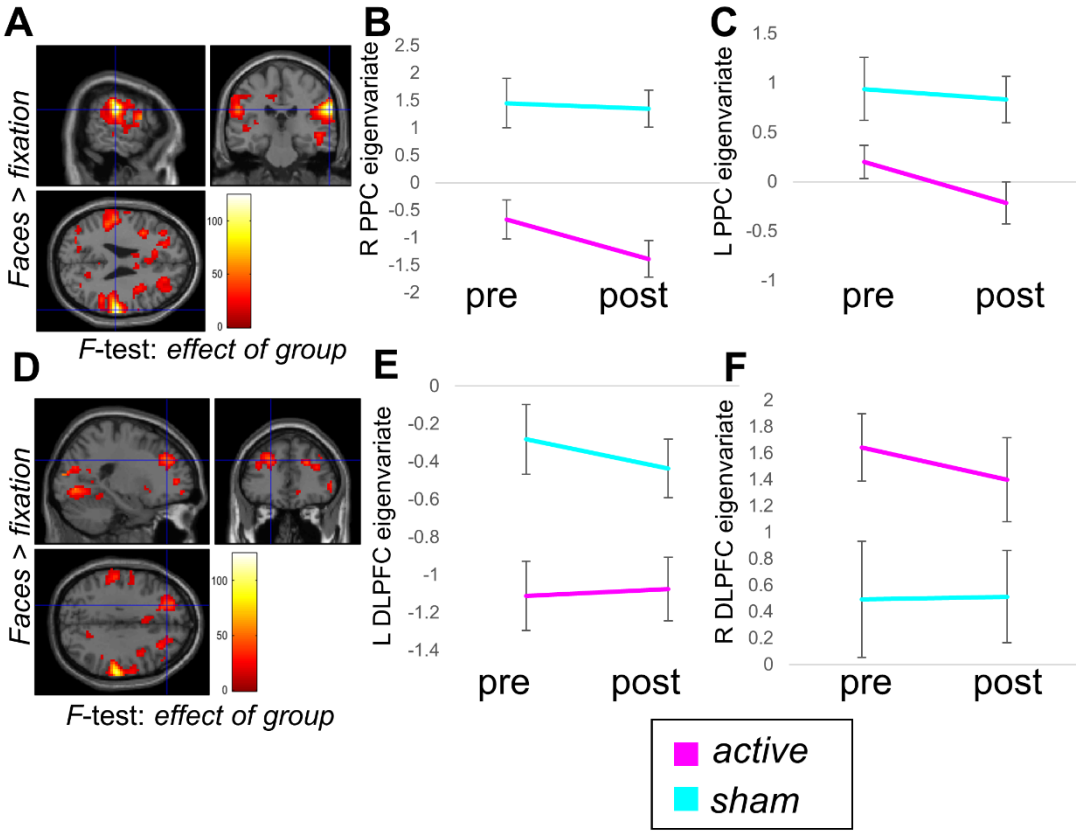

Figure 5.7. Effect of intervention on whole-brain activation (emotion processing). Whole-brain significant group differences in the faces>fixation contrast. A: F-test for effect of group; crosshairs in peak coordinate of right posterior parietal cortex (rPPC) cluster (p<0.001, voxel-level corrected); B, C: Plotted eigenvariate of clusters in right (B) and left (C) PPC pre- and post-intervention, separated for active (magenta) and sham (cyan) tDCS conditions. D: F-test for effect of group; crosshairs in peak coordinate of left dorsolateral prefrontal cortex (DLPFC) cluster (p=0.002, voxel-corrected). E, F: Plotted eigenvariate of clusters in left (E) and right (F) DLPFC pre- and post-intervention, separated for active (magenta) and sham (cyan) tDCS conditions. L=left; R=right. Overlays are thresholded at p<0.001, uncorrected, minimum cluster size k=4 and colour bars indicate F-values.

		p (cluster-corrected)	Extent	*p* (voxel-corrected)	F(1,31)	X	Y	Z	region	direction
faces > fixation	*day*	0.707	11	0.657	21.65	21	-40	14	R fusiform	Day 2 > day 1
		0.246	25	0.718	20.96	-30	-55	-13	L fusiform	Day 1 > day 2
		0.500	16	0.779	20.24	-30	-55	5	L occipital	Day 2 > day 1
		0.939	5	0.866	19.08	36	-49	-10	R fusiform	Day 2 > day 1
		0.620	13	0.909	18.39	-48	-1	2	L premotor	Day 1 > day 2
		0.874	7	0.953	17.43	-33	29	-10	L VLPFC	Day 1 > day 2
		0.963	4	0.982	16.33	3	2	32	R dACC	Day 1 > day 2
		0.794	9	0.986	16.12	30	-79	-16	R occipital	Day 1 > day 2
		0.874	7	0.994	15.4	-45	-70	-10	L occipital	Day 2 > day 1
		0.874	7	0.994	15.38	30	-73	-4	R occipital	Day 1 > day 2
		0.963	4	0.996	15.21	24	14	50	R DLPFC	Day 1 > day 2
	group	<0.001	2425	<0.001	124.21	63	-25	26	R PPC	Sham > active
		<0.001	1015	<0.001	98.83	-48	-67	17	L angular gyrus	Sham > active
		<0.001	763	<0.001	58.06	-54	-25	26	L PPC	Sham > active
		<0.001	313	0.002	51.74	-21	38	32	L DLPFC	Sham > active
		0.081	39	0.004	48.15	-36	11	23	L VLPFC	Sham > active
		<0.001	132	0.013	42.08	24	38	29	R DLPFC	Active > sham
		0.004	82	0.075	33.49	-21	50	5	L frontopolar	Sham > active
		0.178	29	0.165	29.46	-3	-94	2	L V1	Active > sham
		0.500	16	0.229	27.8	24	17	-19	R VLPFC	Sham > active
		0.289	23	0.23	27.78	-51	-4	5	L premotor	Sham > active
		0.001	109	0.252	27.29	-6	-34	44	L posterior cingulate	Sham > active

Table 5.4 Emotion processing task: whole brain results (1). Whole-brain results from flexible factorial for emotion processing task (thresholded at $p<0.001$, uncorrected) for both main effects (day, i.e. pre- versus post-intervention; group, i.e. active versus sham tDCS) and interaction effect. R=right; L=left; dACC=dorsal anterior cingulate cortex; V1=primary visual cortex; PPC=posterior parietal cortex; VLPFC=ventrolateral prefrontal cortex; DLPFC = dorsolateral prefrontal cortex.

		p (cluster-corrected)	Extent	*p* (voxel-corrected)	F (1,31)	X	Y	Z	region	direction
faces> fixation (cont.)	*group (cont.)*	0.963	4	0.324	25.97	33	-64	29	R occipital	Sham > active
		0.500	16	0.326	25.93	6	-49	20	R posterior cingulate	Sham > active
		0.794	9	0.355	25.47	30	-55	-19	R fusiform	Active > sham
		0.835	8	0.419	24.54	27	-70	-22	R cerebellum	Active > sham
		0.463	17	0.459	24.01	6	5	23	R dACC	Active > sham
		0.429	18	0.520	23.25	42	38	35	R DLPFC	Active > sham
		0.874	7	0.522	23.21	-18	14	50	L premotor	Active > sham
		0.227	26	0.581	22.52	18	-61	29	R posterior cingulate	Sham > active
		0.500	16	0.616	22.13	-48	-49	-25	L fusiform	Sham > active
		0.060	43	0.618	22.1	-51	-10	-7	L STG	Sham > active
		0.429	18	0.786	20.15	-9	5	20	L caudate	Active > sham
		0.909	6	0.817	19.76	-54	29	-1	L VLPFC	Sham > active
		0.874	7	0.818	19.75	15	41	-7	R VMPFC	Sham > active
		0.751	10	0.82	19.72	-24	17	-7	L putamen	Sham > active
		0.939	5	0.875	18.95	-21	-58	17	L vis. assoc.	Sham > active
		0.707	11	0.882	18.83	18	17	2	R caudate	Sham > active
		0.874	7	0.9	18.54	15	56	-10	R rostral PFC	Sham > active
		0.963	4	0.926	18.05	27	-94	2	R vis. assoc.	Active > sham
		0.939	5	0.994	15.49	-33	-25	8	L insula	Sham > active
		0.963	4	0.997	14.97	63	-28	-7	R lat. temp.	Sham > active
	*day * group*	0.874	7	0.723	20.90	-30	-49	2	L occipital	Active ↑ Sham ↓

Table 5.4 Emotion processing task: whole brain results (2). Whole-brain results from flexible factorial for emotion processing task (thresholded at $p<0.001$, uncorrected; minimum cluster size=4) for both main effects (day, i.e. pre- versus post-intervention; group, i.e. active versus sham tDCS) and interaction effect. R=right; L=left; dACC=dorsal anterior cingulate cortex; STG=superior temporal gyrus; PFC=prefrontal cortex; VMPFC=ventromedial PFC; VLPFC=ventrolateral PFC; DLPFC = dorsolateral PFC.; vis=visual; assoc.=associative; lat.=lateral; temp.=temporal.

		p (cluster-corrected)	Extent	*p* (voxel-corrected)	F(1,31)	X	Y	Z	region	direction
happy > neutral	*day*	0.909	6	0.805	20.38	-30	-22	26	WM	Day 1> day 2
		0.275	22	0.837	19.95	51	38	-10	R OFC	Day 1 > day 2
		0.639	12	0.889	19.17	-24	-16	44	L SFG	Day 1 > day 2
		0.941	5	0.957	17.74	3	-40	17	R post. cing.	Day 1 > day 2
		0.966	4	0.987	16.48	36	-64	26	R angular gyrus	Day 1 > day 2
		0.966	4	0.998	14.99	0	-40	5	Lat. ventricle	Day 1 > day2
	group	0.087	35	0.095	32.83	-15	11	50	L premotor	Active > sham
		0.941	5	0.676	21.91	24	-28	44	R prim. sensory	Active > sham
		0.966	4	0.832	20.02	15	5	44	R dACC	Active > sham
		0.941	5	0.988	16.44	12	20	53	R SMA	Active > sham
	*day * group*	0.547	14	0.902	18.95	57	-1	-19	R lat. temp.	Active ↑ Sham ↓
		0.735	10	0.997	15.40	-42	14	35	L DLPFC	Active ↑ Sham ↓
		0.966	4	0.997	15.36	-12	65	8	L FPC	Active ↑ Sham ↓
fearful > neutral	*day*	0.783	9	0.289	27.05	-24	-31	-22	L fusiform	Day 1 > day 2
		0.966	4	0.995	15.73	-3	65	17	L FPC	Day 1 > day 2
	group	0.303	21	0.588	22.88	30	-7	14	R insula	Sham > active
		0.829	8	0.955	17.77	42	-52	8	R fusiform	Sham > active
		0.909	6	0.987	16.45	30	-52	-16	R fusiform	Sham > active
	*day * group*	0.871	7	0.957	17.72	-33	-1	26	L PCG	Active ↑ Sham ↓

Table 5.4 Emotion processing task: whole brain results (3). Whole-brain results from flexible factorial for emotion processing task (thresholded at $p<0.001$, uncorrected; minimum cluster size=4) for both main effects (day, i.e. pre- versus post-intervention; group, i.e. active versus sham tDCS) and interaction effect. R=right; L=left; WM=white matter; OFC=orbitofrontal cortex; SFG=superior frontal gyrus; lat.=lateral; prim.=primary; post.=posterior; cing.=cingulate; dACC=dorosal anterior cingulate cortex; SMA=supplementary motor area; temp.=temporal cortex; DLPFC = dorsolateral prefrontal cortex; FPC=frontopolar cortex; PCG=precentral gyrus.

	Effect								Direction
		p (cluster-corrected)	Extent	*p* (voxel-corrected)	F(1,31)	X	Y	Z	region	
Faces > fixation	day	none								
	group	0.020	5	0.001*	28.91	-39	14	26	L DLPFC	Sham > Active
	day * group	none								
Fearful > neutral	day	none								
	group	none								
	day * group	none								
Happy > neutral	day	none								
	group	none								
	day * group	0.023	4	0.038	15.40	-42	14	35	L DLPFC	Active ↑ Sham ↓

Table 5.5 Emotion processing task: small-volume corrected results. Small-volume corrected results of flexible factorial for emotion processing task (p<0.001, uncorrected, cluster-forming threshold=4) for both main effects (day, i.e. pre- versus post-intervention; group, i.e. active versus sham tDCS) and interaction effect, for all ROIs of interest (left and right amygdala; sgACC; left DLPFC). L=left; DLPFC = dorsolateral prefrontal cortex. *=remained significant after correction for multiple comparisons (N=4 ROIs).

5.5 Discussion

We conducted the first RCT of tDCS combined with CBT for depression. We hypothesised that tDCS would enhance the therapeutic effect of CBT, compared to sham stimulation combined with CBT. We show a modest and non-significant effect of the combined intervention on our primary outcome measure, clinical response on the HAM-D. Although the trial provides evidence for the safety and feasibility of augmenting CBT with tDCS for depression, we did not find a substantial effect of tDCS on any mood or cognitive measure. Specifically, we failed to detect any advantage of tDCS over sham on our secondary outcome measures, including self-report measures of mood, anxiety, anhedonia, and performance on the n-back task.

We found a substantial effect of psychological intervention (irrespective of active or sham stimulation) on DLPFC activation during the n-back working memory task, which would be consistent with the notion that the DLPFC plays a role in in CBT. However, it must be noted that this activation change did not differ between active and sham groups and cannot be distinguished from a simple effect of familiarity with the task (i.e. a practice effect). Whole-brain analyses revealed a significant interaction between stimulation group and time on activation in the right PPC during n-back performance: activation increased from pre- to post-intervention only in the active stimulation group (with a non-significant decrease in the sham group). In the emotion processing task, we found a similar pattern in the left DLPFC (both using *a priori* ROI approach collapsing across both emotions, and using a whole-brain analyses for the happy>neutral faces contrast). Activation increased non-significantly over time in the active group, but decreased significantly in the sham group.

5.5.1 Possible interpretations of null clinical effect

There are several possible interpretations of our null clinical finding. Augmenting CBT with tDCS was a logical extension from findings that tDCS successfully enhances the antidepressant effect of cognitive control training (Brunoni et al., 2014a; Segrave et al., 2014). However, the intervention itself had never been tested, so the most straightforward interpretation is that tDCS does not enhance the efficacy of CBT.

That said, in our study, the odds ratios between active and sham condition groups were relatively large (ITT analysis: response: 2.16; remission: 3.65), and with only 39 patients in the trial our study was underpowered to detect all but very large effects. This is somewhat substantiated by the difference in mood improvements seen under tDCS for depression between earlier findings (i.e., (Fregni et al., 2006a), who reported ~60% improvement in the active condition (~14% in sham)), and more recent studies (i.e., (Loo et al., 2012), who reported 28% improvement in the active condition (~11% in sham)). However, this possibility would be strengthened if there were also any effect of tDCS on our secondary measure of depression, BDI, which we did not find. It is worth noting there are important differences between the HAM-D and the BDI as measures of depression that could have contributed to this discrepancy, most notably its self-report nature: for instance, patients with low extraversion and high neuroticism are more likely to endorse depressive symptoms on the BDI compared to the HAM-D (Schneibel et al., 2012).

There are other aspects of our design that might have influenced this null finding. It is worth noting that many previous trials have used different stimulation montages. While the anodal electrode is placed, like ours, over the left DLPFC in many

depression trials, a bifrontal montage is often used, with the cathodal electrode over the right DLPFC (Brunoni et al., 2013); in others, the cathodal electrode is placed over the right contralateral orbit (Loo et al., 2012). We placed the cathodal electrode over the ipsilateral deltoid in order to minimize effects of the cathodal electrode on the brain (Priori et al., 2008; Wolkenstein and Plewnia, 2013); however, it is possible the effects of the cathodal electrode on the brain contribute to an antidepressant response (or simply that our montage elicits a less optimal current distribution for depression).

A second factor that could have contributed to a null result was stimulation frequency. Our stimulation sessions were delivered at a relatively low frequency (at least 6 days between tDCS sessions), while previous trials of tDCS in depression typically deliver stimulation daily or near-daily (Boggio et al., 2008; Brunoni et al., 2013; Fregni et al., 2006a; Loo et al., 2012). However, our trial sought to be a pragmatic test of tDCS as an adjunct to standard CBT treatment, so we adhered to weekly CBT sessions, as is typical practice in the UK NHS for outpatients with moderate-to-severe depression (National Institute for Health and Clinical Excellence, 2009).

A final potential contributor was that we were restricted to 1 mA of stimulation, as advised by our ethics committee, whereas other trials have typically used 2 mA. For example, a previous study successfully combining tDCS and sertraline delivered 10 sessions of 2 mA current over a two week period, followed by two more sessions (delivered every other week for the next four weeks) (Brunoni et al., 2013). Compared to that study, our patients received substantially less stimulation current. This is important because a recent meta-analysis found that the efficacy of DLPFC

tDCS in depression was related to stimulation current and duration (Brunoni et al., 2016).

5.5.2 Null effect of tDCS on n-back performance

All of the above factors could have also contributed to the null effect of tDCS on n-back task performance. However, there was also a surprising effect of tDCS on n-back behaviour, though only when measured inside the scanner: patients receiving sham stimulation improved significantly more than those receiving active stimulation. To our knowledge, no comparable findings of apparent deleterious effects of multiple-session anodal DLPFC tDCS have been reported. Several other studies (with varying montages and stimulation protocols) have shown no additional enhancing effects of multiple tDCS sessions on the n-back task (Lally et al., 2013; Martin et al., 2013; Talsma et al., 2017). Additionally, a recent meta-analysis found that anodal DLPFC tDCS stimulation has no offline effect (i.e., an effect not observed during tDCS administration itself) on working memory accuracy in neuropsychiatric populations (and only a trend for improvements in healthy populations) (Hill et al., 2016). One study in this meta-analysis even reported numerically (but not significantly) worse n-back performance in patients with schizophrenia following a session of active 1 mA anodal stimulation (with a numerical, non-significant improvement in the sham group) (Hoy et al., 2013). Therefore, a combination of the multiple sessions, neuropsychiatric population, offline measurement and the other elements of our trial that were relatively distinct (as discussed in the previous section) could all have contributed to this surprising result. If even the acute effects of tDCS on n-back performance are very variable (Horvath et al., 2015), our sample may simply have shown a heretofore unseen detrimental effect of active tDCS on

offline working memory (i.e., working memory measured after tDCS delivery, as opposed to the “online” effects of tDCS on working memory, measured at weekly stimulation sessions).

5.5.3 Effects of tDCS on neural activation

To our knowledge, this was the first tDCS trial for depression to include fMRI, as well as clinical and cognitive measures. We found a substantial effect of psychological intervention (irrespective of tDCS condition) on DLPFC activation, which increased in both study arms over time and was indistinguishable from a sample of healthy controls at the end of the trial (while at baseline patients showed DLPFC hypoactivation). These results accord with the only other CBT trial to measure fMRI activation: in a small sample (N=9), prefrontal activation during the digit-sorting task increased after a 16-week CBT course, following baseline hypoactivation (Siegle et al., 2007a). Low DLPFC activation in depression has been suggested to result in impaired cognitive control, contributing to an impaired ability to inhibit attention toward negative stimuli, dysfunctional emotional processing, and rumination (Disner et al., 2011). CBT is thought to counteract patients’ perceived accuracy of negative schema, ameliorating cognitive biases (Butler et al., 2006). Furthermore, cognitive control training increases DLPFC activation during cognitive tasks (Siegle et al., 2007b); training on another prefrontal executive task, the n-back task, could certainly contribute to our finding of increased DLPFC activation after the intervention.

However, we found no effect of stimulation condition on DLPFC activation during working memory. Instead, we found preliminary results (that we did not anticipate) for a differential effect of tDCS on right PPC activation which survived whole-brain correction for multiple comparisons: activation increased from pre- to post-

intervention only in the active stimulation group, but did not (and indeed was numerically decreased) in the sham group. The PPC is reliably activated in fMRI studies of the n-back task (Owen et al., 2005), including in our whole-brain activation results for the same contrast in the sample reported in Chapter 4. Additionally, in the left parietal cortex, perfusion was reported to increase during anodal tDCS of the DLPFC (Stagg et al., 2013). Therefore, it is plausible that the increase we observed over time in the active group reflects a true change in activation elicited by the combination of active tDCS with the n-back task at weekly sessions. However, it should be noted that this did not seem to result in improved performance on the task itself.

The stimulation groups also differed in terms of neural activation during emotional face processing, particularly in the left DLPFC (in the ROI results, collapsing across both emotion contrasts; in the whole-brain SVC results, in the happy>neutral contrast). While patients assigned to sham stimulation showed significantly decreased activation over time in the left DLPFC, this was not the case in those assigned to active stimulation, in whom activation increased over time (though this was only marginally significant). This tentatively showed an effect of active tDCS on left DLPFC activation during emotion processing (but not apparently during working memory) that differs from CBT combined with sham stimulation; interestingly, a similar pattern was observed in the amygdala. Since there were no significant group differences on clinical scores, this differential effect may reflect a neural mechanism of tDCS that our other measures (clinical and cognitive) could not capture.

However, the interpretation of the above finding is complicated by the significant and widespread difference between treatment arms observed in the faces>fixation

contrast, which was already present at baseline. It is possible that this could have contributed to the other group differences observed in this task, albeit in contrasts that did not show group differences at baseline. Presumably these differences arose from imperfect randomization (despite no observed differences in our clinical and demographic measures). This may have been exacerbated by the asymmetric drop-out between groups (1 active; 5 sham, though this difference was not significant): importantly, no group differences were significant on the faces>fixation contrast in a 2-sample t-test at baseline with the full (N=20 active; N=19 sham) sample. One possible interpretation of this finding is that patients with lower activation to faces (relative to fixation) are more likely to drop out of psychotherapy – unfortunately our sample was too small to provide a meaningful test of this hypothesis, but it would be worth examining in larger studies.

5.5.4 Conclusion

Our data do not provide immediate support for the use of tDCS to augment CBT in depression. Contrary to our hypotheses, we found no effect of tDCS on scales of depression, anxiety, and anhedonia, or on neural and cognitive measures of working memory. We identified a strong effect of psychotherapy (irrespective of tDCS condition) on DLPFC activation, and some preliminary effects of active tDCS on left DLPFC and amygdala activation during emotion processing. It is possible that the intervention itself (the timing, stimulation parameters, and protocol of administration) may have affected the results; and it is also very likely that our study was underpowered, at least for the primary outcome measure.

Although the above mentioned caveats are important, another possibility is that tDCS has a variable effect that we may be able to predict with baseline measures of

cognitive and neural processing. There is evidence that baseline neural activation (measured with task-based and resting state fMRI, as well as PET) can predict response to common treatments for depression, including antidepressant medication and CBT (Roiser et al., 2012) as well as ECT (Van Waarde et al., 2015). Could it also predict therapeutic response to tDCS? It is this prospect that I explore in Chapter 6.

Chapter 6. Predicting response to noninvasive brain stimulation and psychotherapy for depression

6.1 Abstract

Transcranial direct current stimulation (tDCS) has been suggested as a putative treatment for depression, but results from clinical trials are mixed. This may be in part due to variability between patients. In other treatment strategies for depression, baseline measurements (including, more recently, neuroimaging measurements) have been shown to predict a patient's likelihood of response (Drysdale et al., 2017; Dunlop and Mayberg, 2014). However, no neuroimaging predictor of treatment response to tDCS for depression has yet been described in an RCT (indeed, to our knowledge, no fMRI predictor has been described for any depression treatment in the context of an RCT). Using regression analyses, we tested whether baseline neural activation measured in fMRI paradigms (working memory and emotion processing) was associated with the degree of depression improvement following an RCT that tested active or sham tDCS combined with CBT (described in Chapter 5). We also examined other predictors of treatment outcome: baseline depression, anxiety, anhedonia, and working memory capacity. The RCT design enabled us to test both specific predictors of response to tDCS/CBT (i.e. in the active stimulation group alone), and general predictors of response to CBT (i.e. across both groups). We hypothesized that activation in the region of stimulation, the left DLPFC (measured during working memory prior to treatment), would predict clinical response to tDCS. The results were consistent with our hypothesis: left DLPFC activation during working memory specifically predicted response to active, but not

sham tDCS. Furthermore, the left DLPFC showed good within-subject reliability between scans several months apart, an important determinant of clinical utility. By contrast, consistent with previous reports (Siegle et al., 2006), right amygdala activation during emotion processing predicted improvement to CBT irrespective of treatment arm; however, it showed low within-subject reliability between scans, raising some uncertainty regarding the interpretation of this finding. An exploratory whole-brain analysis also revealed two significant clusters, in the left rostral PFC and left posterior parietal cortex (PPC) that were both predictive of clinical outcome irrespective of treatment arm. In summary, we report a potential predictor of response to tDCS combined with CBT in depression, providing a possible means of identifying future responders to this intervention with fMRI. This work additionally adds to previous findings describing pre-treatment neural activations associated with a favourable response to CBT.

6.2 Introduction

The standard procedure for identifying appropriate treatments for a group of patients involves running an RCT, and reporting an aggregate (group) effect, as employed in Chapter 5. However, this may mask important and informative differences between patients. A key priority for medical research is identifying objective measures (or 'biomarkers') that may help to optimize treatment selection (Dunlop and Mayberg, 2014). Outside of psychiatry, there have been several notable successes on this front, chief among them the use of specific breast tumour biomarkers (oestrogen; epidural growth factors) to select or avoid particular chemotherapy treatments (Dunlop and Mayberg, 2014; Ellsworth et al., 2010).

To identify outcome predictors, an RCT needs to include relevant mechanistic measurements prior to randomisation. In psychiatry, where most disorders are of unknown aetiology, trials typically measure only symptoms at baseline. Outside RCTs there have been substantial efforts to characterize response to treatment according to symptom measures. These have yielded varying degrees of success: for instance, anhedonia (and a cluster of associated symptoms related to interest and activity) is generally predictive of antidepressant non-response (McMakin et al., 2012; Uher et al., 2012), while depression subtype seems not to be (Arnow et al., 2015). Several factors other than symptom profile, such as age, severity, and chronicity have been consistently reported to predict poor response to antidepressant treatment (Hamilton and Dobson, 2002). However, these predictors usually provide only a general marker of treatment responsiveness, rarely predicting response to specific treatments, or an active intervention relative to placebo (Frank et al., 2011; Roiser et al., 2012) (though one notable exception is the use of

machine-learning models to identify patients likely to respond to specific antidepressants (Chekroud et al., 2016, 2017)).

Over the past 15 years, as neuroimaging techniques have revealed the brain circuits consistently implicated in depression, the suggestion has emerged that responsivity in these regions might provide useful information about mechanistic heterogeneity in the disorder, and insight into differential treatment response (Dunlop and Mayberg, 2014; Roiser et al., 2012). Ideally, a potential predictor would be related to the pathophysiology of depression (Dunlop and Mayberg, 2014). A number of groups have identified a network of regions where activation is associated with treatment response.

Two regions in particular have emerged as strong candidates for predictors of treatment response in depression: the anterior cingulate cortex, particularly the rostral and subgenual (sgACC) portions, and the amygdala. Early work using PET indicated that anterior cingulate hypermetabolism may predict better response to antidepressant medication (Mayberg et al., 1997) and sleep deprivation therapy (Wu et al., 1999). More recent PET work has shown an effect in the opposite direction, with nonresponders to both venlafaxine and CBT showing pretreatment hypermetabolism in the pregenual/sgACC (Konarski et al., 2009). This study (as well as the Mayberg 1997 paper) suffered from a small sample size (N<10 in each group), limiting its ability to reveal treatment-specific activation. A small number of other PET studies have compared brain metabolism changes in responders to psychological therapies with metabolism changes in antidepressant medication responders (Brody et al., 2001a; Kennedy et al., 2007; Martin et al., 2001). Two studies compared medication (paroxetine and venlafaxine) responders with IPT

responders. The first found both interventions decreased anterior cingulate gyrus activation (Brody et al., 2001a); the second found both interventions increased basal ganglia metabolism, but that only interpersonal therapy increased posterior cingulate metabolism (Martin et al., 2001). However, both studies showed greater clinical response in the medication group relative to IPT, and neither study used random treatment assignment.

One of the few RCTs to explore this question found changes in metabolism in the posterior cingulate differentiated venlafaxine and CBT treatment responders: venlafaxine response was associated with increases in the posterior cingulate cortex over the course of the 16-week treatment, while response to CBT was associated with decreased activation in the posterior cingulate (Kennedy et al., 2007). Another RCT from the same group found that insula hypometabolism was associated with remission to CBT and poor resonse to escitalopram, while insula hypermetabolism was associated with remission to escitalopram and poor response to CBT (McGrath et al., 2013). However, these studies are limited in several respects, most notably that all examine resting-state metabolism, rather than task-evoked brain responses during cognition. Instead, the use of disorder-relevant cognitive tasks during task-related fMRI has revealed several regions that may predict response to specific treatments.

In the fMRI literature, the sgACC and amygdalae have been most frequently implicated as potential baseline predictors of treatment response. Pre-treatment activation in the perigenual anterior cingulate cortex (ACC; including rostral and sgACC), particularly during emotion processing, may predict differential response to standard antidepressant treatment (Chen et al., 2007; Davidson et al., 2003;

Keedwell et al., 2009, 2010). Pre-treatment perigenual ACC deactivation to negative stimuli has been reported to predict worse response to antidepressant treatment with two different medications, fluoxetine (Chen et al., 2007) and venlafaxine (Davidson et al., 2003). By contrast, in other studies sgACC deactivation to negative stimuli predicted *better* response to cognitive behavioural therapy (Fu et al., 2008a; Siegle et al., 2006) and behavioural activation therapy (Dichter et al., 2010). As with the PET findings, however, these studies usually lack comparison groups (or, if two treatments are used, treatment assignment is non-random). The amygdala, in contrast to the sgACC, may represent a more non-specific predictor: heightened amygdala activation during inhibitory control (Langenecker et al., 2007) and negative information processing (Siegle et al., 2006, 2007a) has been reported as a predictor of favourable treatment response in depression irrespective of treatment approach, with positive findings for both antidepressant medication and CBT, respectively.

Most fMRI studies of putative predictors of treatment response in depression have focused on activation to emotional faces (Frodl et al., 2010; Fu et al., 2008a, 2008b, Keedwell et al., 2009, 2010). Despite robust activation when averaging across individuals, and the evidence discussed above that activation may differentiate between responders and non-responders (Fu et al., 2008a; Keedwell et al., 2009, 2010; Langenecker et al., 2007), many authors have acknowledged that clinically relevant prognostic markers require high measurement accuracy at the level of the individual (Fu et al., 2013). To achieve this with fMRI, the reliability of measurement of BOLD responses should be good. We have recently reported that sgACC and amygdalae activation in response to emotional faces has quite low within-subject reliability, while a control region (the FFA) showed high reliability (Nord et al., 2017a). Therefore, it is possible that more reliable predictors might be found in other

brain regions using paradigms that do not focus on emotional face processing (e.g., (Walsh et al., 2007)).

Another cognitive activation paradigm frequently investigated in depression is the n-back working memory task. Previous studies have found fair-to-good within-subject reliability of the BOLD signal in the n-back task in healthy volunteers (Plichta et al., 2012), and, measuring graph theoretical properties, superior global and local network properties of the n-back task relative to an emotional face processing task (Cao et al., 2014). Whether this would extend to psychiatric patient populations remains to be determined. One of the main regions of activation of the n-back task, the DLPFC, has been less frequently implicated as a putative predictor of treatment response for standard interventions in depression, though there are some exceptions: lower baseline activation in the left middle frontal cortex (as well as dorsal anterior cingulate and lateral temporal cortices) during the n-back task was associated with improved clinical outcome following treatment with fluoxetine (Walsh et al., 2007). A recent systematic review of rTMS treatments for depression showed that clinical response was related to baseline cerebral blood flow in the frontal lobe (Silverstein et al., 2015). A small study included in this meta-analysis (13 patients, 6 responders) reported greater baseline resting-state cerebral perfusion in the left DLPFC was associated with clinical response to left DLPFC rTMS (Weiduschat and Dubin, 2013). However, other studies in the meta-analysis reported the opposite (Kito et al., 2008) or no significant relationship (Kito et al., 2012).

Other studies have suggested that the effect of tDCS on the DLPFC may depend on baseline cortical activity, a source of variability in experimental effects induced by DLPFC tDCS (Tremblay et al., 2014). Recently, a small study showed a machine

learning algorithm could accurately classify clinical response to tDCS in 8 out of 10 depressed patients (5 tDCS responders) using resting-state EEG measures (Al-Kaysi et al., 2017). In this study, the algorithm showed above chance accuracy when using spectral power in frontal scalp channels, although due to the machine learning approach, the direction of activity associated with better response was not reported. The channel pair identified corresponded with regions stimulated by tDCS, according to computer modelling of their tDCS montage (Bai et al., 2014). However, in such a small study, without replication, the chance of model over-fitting is very high.

In depression, it is still unusual to use neural or cognitive measures in the context of an RCT. One notable exception is the iSPOT-D trial (Etkin et al., 2015; Williams et al., 2015), which found that in a subgroup of cognitively-impaired depressed patients, reduced performance on a number of cognitive tests predicted treatment non-response following citalopram, but not sertraline or venlafaxine treatment (Etkin et al., 2015); however, it should be noted that this study did not include a placebo arm). More typically, attempts to identify predictors of treatment response are conducted post-hoc and are not incorporated into RCTs. This introduces the most important limitation of most findings in the literature: Without a comparison arm, studies cannot separate treatment-nonspecific from treatment-specific predictors.

Our clinical trial combined CBT with tDCS (or sham tDCS) (Chapter 5), and allowed us to test for treatment-specific predictors for tDCS. We hypothesized that greater baseline task-evoked activation in the location of stimulation, the left DLPFC, would specifically predict response to tDCS, over and above general response to CBT. Activation was measured during an fMRI working memory paradigm (the n-back task) that reliably evokes left DLPFC activation; this activation was lower in the

depressed patients compared with healthy controls (Chapter 4), and increased over the course of this intervention in both treatment arms (Chapter 5). We also hypothesized that greater amygdala activation during fearful face processing would predict CBT response, as reported in prior studies (Siegle et al., 2006, 2007a), irrespective of stimulation condition. This is motivated by the hypothesis that CBT is most useful to patients with heightened amygdala activity, potentially by improving emotional control in patients with particularly sustained emotional reactivity (Siegle et al., 2006).

6.3 Methods

We analysed data from N=33 patients who met criteria for a diagnosis of major depressive disorder (MDD), all of whom completed the RCT combining tDCS and CBT described in Chapter 5. Our aim in the present chapter was to determine which baseline variables could predict clinical response, across both groups and specifically for the active stimulation group. Measured variables were: mean activation across our task-specific ROIs (left and right DLPFC activation during the n-back task (contrast: 3-back>1-back); left and right amygdalae and sgACC activation during the emotion processing task (contrasts: fearful>neutral and happy>neutral)); working memory performance, quantified as d' in the 3-back condition of the n-back working memory task; and baseline symptoms: depression (HAM-D and BDI), anxiety (BAI), and anhedonia (SHAPS). All aspects of data collection, including recruitment, behavioural testing, trial design, and MRI pre-processing steps are described in Chapter 5.

6.3.1 Analysis

We first mean-corrected all baseline variables: right and left DLPFC activation, right and left amygdala activation, sgACC activation, n-back d', SHAPS score, BAI score, and HAM-D.

All models sought to predict the same outcome variable: the degree of clinical improvement, quantified as percent change in HAM-D score from baseline to final assessment. We tested this in two ways: our primary analyses tested whether pre-randomization activation in each region of interest (ROIs: the DLPFC during the n-back task; the amygdalae and sgACC during the emotional faces task) could predict degree of clinical improvement (single-predictor model). In addition to activation over the ROI, each regression model included the fixed effect of stimulation group (active or sham). If the single-predictor model was significant, we also conducted sensitivity analyses (described below) that tested whether any significant predictor survived inclusion of additional baseline variables to the model (HAM-D, BAI, and SHAPS scores, as well as baseline n-back performance). For each contrast (for the n-back task: 3-back>1-back; for the emotion processing task: happy>neutral and fearful>neutral), we also ran an exploratory whole-brain analysis to identify activation predictive of response to treatment in regions we had not hypothesised *a priori*.

6.3.1.1 Sensitivity analyses

For regions with significant single-predictor models, we conducted sensitivity analyses. Here, we first tested for multicollinearity for each predictor separately; we assumed evidence of multicollinearity if the variance inflation factor (VIF) between any two variables was greater than 3. Next, we constructed the model including all

six predictors (if there was no evidence for multicollinearity) and their interactions with stimulation group. If the overall model was not significant, we did not proceed with stepwise regression. If the overall model was significant, we used a backwards stepwise regression technique to test which of the measures significantly predicted clinical response (percent change in HAM-D). Using backward step-wise elimination, we removed any variables with $p>0.1$, until all variables, or their interactions with stimulation group, predicted percent change in HAM-D sufficiently (i.e., had a p value exceeding 0.1). We then report these significant predictor variables.

6.3.1.2 Assessing the reliability of significant predictors

Again for regions with significant single-predictor models, we also assessed within-subject reliability of activation between the baseline scan and the post-intervention scan. Note that although we expected (and have reported in Chapter 5) group-level changes between baseline and post-intervention activation, our measure of within-subject reliability assesses only the relative consistency of activation between scans (i.e., the subjects with greater activation on day 1, relative to the rest of the group, are also those with greater activation on day 2). Particularly in the case of an interventional design such as this, we would not expect absolute agreement between individual subjects' activation.

We calculated intra-class correlation coefficients (ICCs) for each ROI that was significantly predictive of response. The ICC is a standard method to quantify the stability of measurements between test and retest sessions (Bennett and Miller, 2010). To calculate ICCs, we used the same approach as in our previous work (Nord et al., 2017a), assessing reliability using ICC(3,1), a 2-way mixed effects ICC, defined by Shrout and Fleiss (Shrout and Fleiss, 1979) as:

ICC(3,1) = BMS-EMS/BMS+(k-1)*EMS

Where BMS = between-subjects mean square; EMS = error mean square; k = number of repeated sessions (i.e., 2 in the case of this RCT).

This can be interpreted as a ratio of variances (Bartko, 1966), with ICCs approaching 1.0 indicating near-perfect correlation between BOLD response parameter estimates between sessions (i.e., before and after the intervention), and ICCs approaching 0 indicating little or no reliability. This approach has also been used in a number of studies assessing the reliability of amygdala activation (Johnstone et al., 2005; Lipp et al., 2014; Plichta et al., 2012; Sauder et al., 2013). The form of ICC we calculated has several important elements: first, the effect of measure (i.e., the scanner) is assumed to be fixed rather than random, while the effects of subjects are assumed to be random. Second, we employ a "consistency" measure of ICC, rather than testing the absolute agreement between days or runs, due to the possibility that participants might habituate to the stimuli over time. Last, we report average measures ICC statistics as the calculation of parameter estimates in fMRI inherently involves averaging over many trials.

We adhere to a conventional interpretation of ICCs to quantify the degree of reliability: ICC<0.4 = poor reliability; 0.4—0.75 = moderate to good reliability; >0.75 = excellent reliability (Fleiss, 1986; Nord et al., 2017a; Plichta et al., 2012). A negative ICC is usually interpreted as a reliability of zero (Bartko, 1976), since the theoretical limits of the ICC are 0—1 (negative values can occur when the within-groups variance exceeds the between group variance, but are outside the theoretical range of the ICC (Lahey et al., 1983)). We also report *p*-values for all reliable activations,

and 95% confidence intervals for all ICCs, obtained from an *F*-test against the null hypothesis.

6.3.1.3 Exploratory whole-brain analyses

For each contrast (nback: 3-back>1-back; emotion processing: fearful>neutral; happy>neutral), we also conducted an exploratory whole-brain analysis. We constructed an independent samples t-test in SPM testing for the effect of group (active or sham) on each contrast, and including our outcome measure, percent change in HAM-D, as a covariate in the model. We report all whole-brain activations associated with response across both groups, and all interactions between group and per cent change HAM-D ($p<0.001$ (uncorrected), minimum cluster size k=4). Whole-brain corrected *p*-values are reported at the cluster and voxel levels. For each contrast, we also report small volume corrected (SVC) results within our task-specific ROIs.

6.3.1.4 Power analysis

In the case of the single-predictor regression models, an N of 33 gave us 84% power to detect a large effect size (f) of 0.6 (given an alpha of 0.05, and 2 groups). In the case of the sensitivity analyses (multiple regression models), we had 83.7% power to detect an effect size of f=0.6 (given an alpha of 0.05, 2 groups, and five covariates (ROI, HAM-D, BAI, SHAPS, and n-back d').

6.4 Results

6.4.1 A priori analysis: left DLPFC

The single-predictor model including only left DLPFC activation and stimulation group was significant overall ($F(3,29)=5.32$, $p=0.005$). In the model, greater baseline left DLPFC activation significantly predicted greater subsequent percent change in HAM-D ($F(1,29)=12.77$, $p=0.001$). The interaction between left DLPFC activation and stimulation group was also significant ($F(1,29)=6.83$, $p=0.014$). Analysing the stimulation groups separately, greater activation in the left DLPFC at baseline was associated with a significantly larger percent reduction in HAM-D in the active stimulation group ($r=0.711$, $p=0.001$), but not in the sham stimulation group ($r=0.205$, $p=0.482$) (see Figure 6.1).

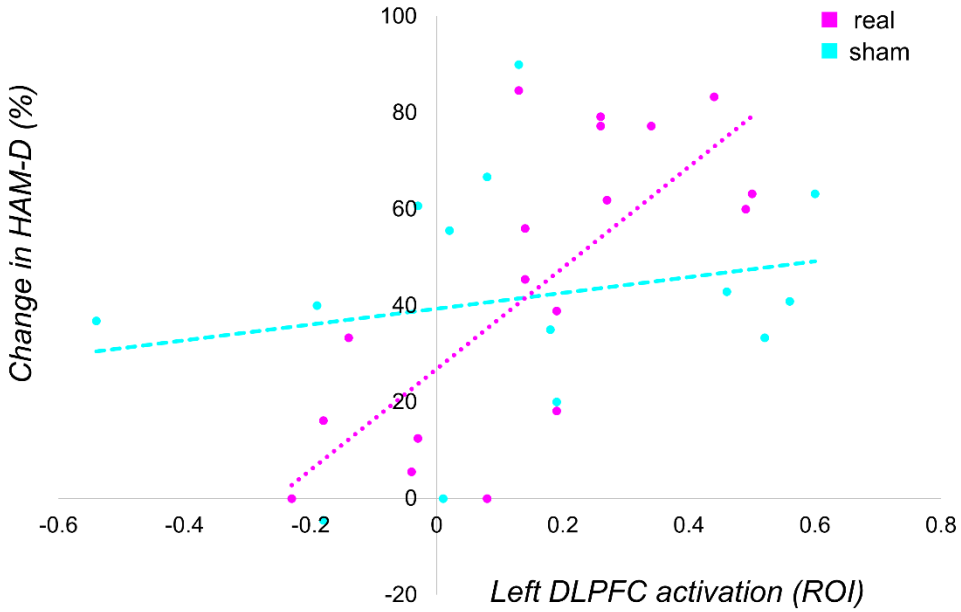

Figure 6.1 Association between DLPFC and mood improvement. The relationship between baseline left dorsolateral prefrontal cortex (DLPFC) activation and response to intervention, measured as percent decrease in Hamilton Depression Rating Scale (HAM-D) score. The interaction between left DLPFC activation and stimulation group was significant ($F(1,29)=6.83$, $p=0.014$).In the group receiving active stimulation (magenta), greater activation in the left DLPFC at baseline was associated with a larger percent change in HAM-D ($r=0.711$, $p=0.001$); this was not the case in sham stimulation group ($r=0.205$, $p=0.482$).

6.4.1.1 Sensitivity analysis: left DLPFC

We then tested the sentitivity of the left DLPFC model. We first iteratively tested for multicollinearity between all independent variables. The variance inflation factor (VIF) did not exceed our threshold of 3 (all VIF<1.5). Therefore, the initial sensitivity model included all six variables: left DLPFC activation, baseline HAM-D, SHAPS, and BAI scores, baseline n-back performance (d'), and stimulation group (dependent variable: percent change in HAM-D score), as well as interactions with stimulation group. The initial model was significant ($F(1,21)=3.46$, $p=0.007$). All variables except SHAPS and n-back performance (or their interaction with stimulation group) were at least marginally predictive of clinical outcome ($p<0.1$). Following our backwards stepwise elimination procedure, we first eliminated SHAPS from the model. The model was still significant ($F(9,23)=3.90$, $p=0.004$), but n-back performance still was

not a significant predictor ($F(1,23)=0.30$, $p=0.591$), nor did its interaction with stimulation group predict outcome ($F(1,23)=0.18$, $p=0.673$). We next eliminated n-back performance from the model. The model remained significant overall ($F(7,25)=5.28$, $p=0.001$), and we lastly eliminated the nonsignificant interaction between HAM-D and stimulation group ($F(1,25)=0.607$, $p=0.443$) to determine the final model, which was significant itself ($F(6,26)=6.15$, $p<0.001$), and where all remaining baseline variables (or their interactions with stimulation group) were significant predictors of clinical outcome.

In the final sensitivity model, left DLPFC activation remained a significant individual predictor of clinical outcome ($F(1,26)=29.90$, $p<0.001$); its interaction with stimulation group also still significantly predicted outcome ($F(1,26)=10.87$, $p=0.003$). Baseline HAM-D was also a significant predictor overall ($F(1,26)=12.38$, $p=0.002$). BAI was only a marginally significant predictor alone ($F(1,26)=3.12$, $p=0.089$), but its interaction with stimulation group was a significant predictor of clinical outcome ($F(1,26)=5.38$, $p=0.029$).

Although baseline HAM-D was a significant positive predictor of HAM-D change in the full model ($p=0.002$), a model including only HAM-D and stimulation group was non-significant ($F(3,29)=0.23$, $p=0.877$), nor was HAM-D a significant predictor independently ($F(3,29)=0.578$, $p=0.453$) or interacting with stimulation group ($F(3,29)=0.193$, $p=0.664$) (see Figure 6.2A) in this model.

Similarly, higher baseline anxiety (BAI) also did not individually predict percent change in HAM-D (with stimulation group as a fixed factor): the full model was not significant ($F(3,29)=0.21$, $p=0.888$); BAI was not a significant predictor independently

(*F*(1,29)=0.024, *p*=0.878) or interacting with stimulation group (*F*(1,29)=0.55, *p*=0.465) in this model, again despite its significant interaction with stimulation group in the full model (*p*=0.029) (note the sign differences in the directions of the non-significant correlations: active (*r*=0.153, *p*=0.533); sham (*r*=-0.125, *p*=0.670)) (see Figure 6.2B).

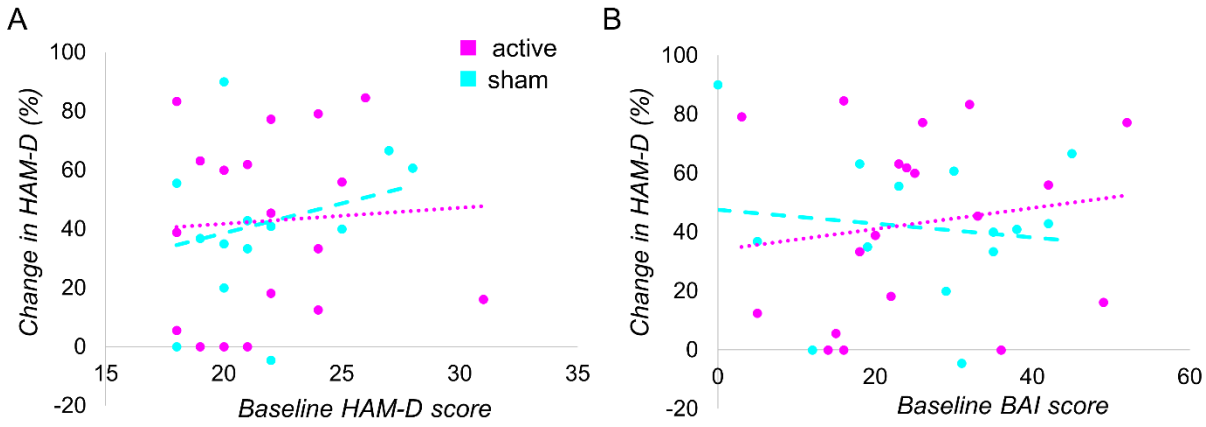

Figure 6.2 Relationship between baseline mood and improvement. A. Baseline HAM-D score was not predictive of subsequent change in HAM-D independently (r=0.127, *p*=0.480); full left DLPFC model: *p*=0.002). B. In the full model, baseline BAI interacted with stimulation group to predict clinical outcome, but was not significant in either group alone. Separately, neither active (*r*=0.153, *p*=0.533) nor sham (*r*=-0.125, *p*=0.670) groups showed a significant relationship with subsequent percent change in BAI.

6.4.1.2 Reliability analysis: left DLPFC

We also quantified the within-subject reliability of left DLPFC activation. Left DLPFC activation showed very good reliability (ICC=0.67, 95%CI=0.33—0.84, *p*=0.001). This was the case in both active (ICC=0.69, 95%CI=0.19—0.88, *p*=0.009) and sham groups (ICC=0.65, 95%CI=-0.08—0.89, *p*=0.034) (see Figure 6.3A).

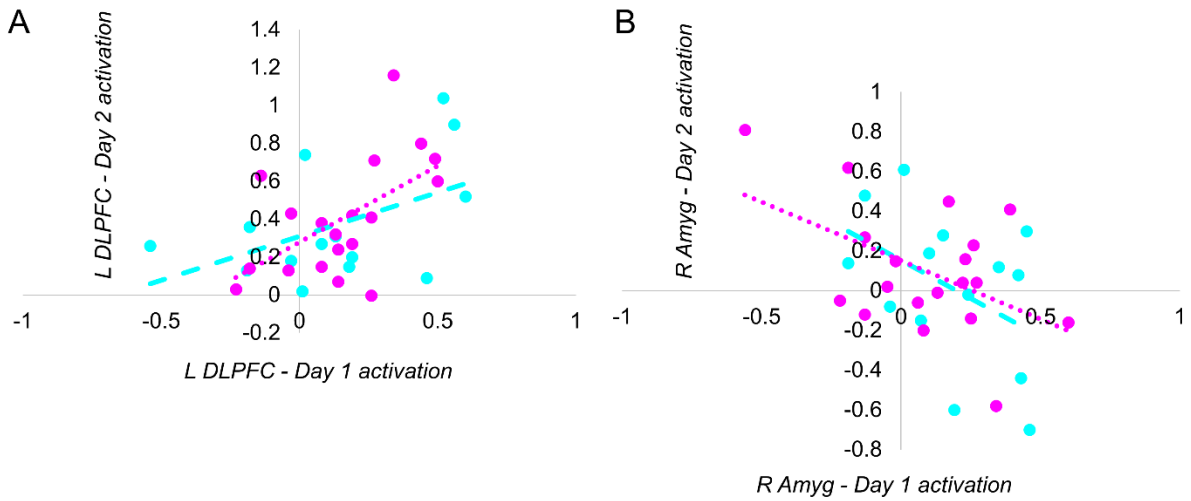

Figure 6.3 Reliability of DLPFC and amydala activation. Distribution of parameter estimates for the left DLPFC (A) and right amygdala (B) on day 1 (pre-intervention) and day 2 (post-intervention). A: in the left DLPFC, within-subject reliability was good (ICC=0.67, 95%CI=0.33—0.84, *p*=0.001) in both active (ICC=0.69, 95%CI=0.19—0.88, *p*=0.009) and sham groups (ICC=0.65, 95%CI=-0.08—0.89, *p*=0.034). B: in the right amygdala, within-subject reliability was very poor (ICC=-1.630, 95%CI=-4.325– -0.299, *p*=0.996), in both active (ICC=-1.83, 95%CI=-6.35– -0.09, *p*=0.984) and sham groups (ICC=-1.26, 95%CI=-6.04– -0.27, *p*=0.923).

6.4.2 A priori analysis: left amygdala (fearful>neutral contrast)

In a model containing only left amygdala activation and stimulation group, left amygdala activation did not predict percent change HAM-D, either alone ($F(1,29)=2.30$, $p=0.140$, or interacting with stimulation group ($F(1,29)=0.57$, $p=0.457$). Therefore, we did not continue with sensitivity or reliability analyses.

6.4.3 A priori analysis: right amygdala (fearful>neutral contrast)

In a model containing only right amygdala activation and stimulation group, higher baseline left amygdala activation was associated with greater percent reduction in HAM-D ($F(1,29)=7.69$, $p=0.010$); its interaction with stimulation group was non- ($F(1,29)=0.54$, $p=0.469$) (see Figure 6.4).

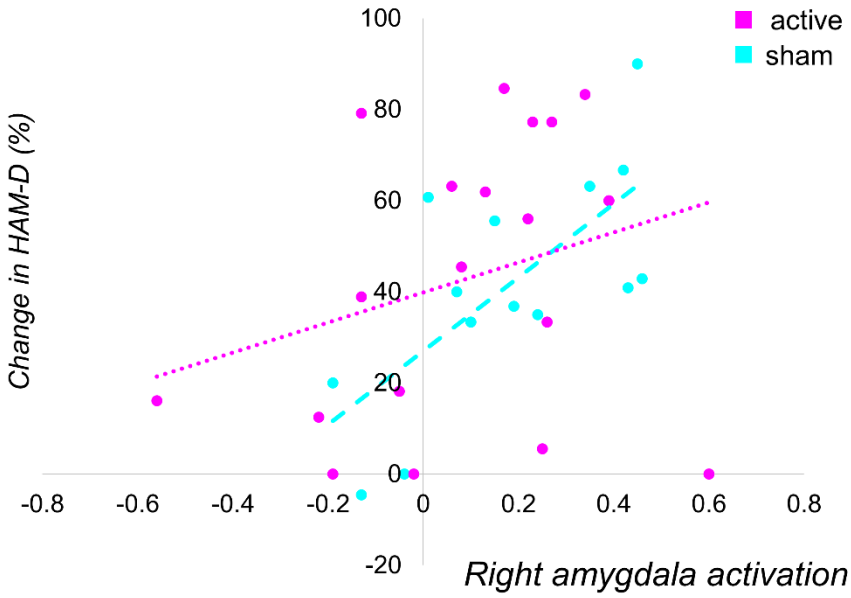

Figure 6.4 Association between right amygdala activation and mood improvement. The relationship between baseline right amygdala activation (to fearful>neutral faces) and response to intervention, measured as percent reduction in Hamilton Depression Rating Scale (HAM-D). Right amygdala activation at baseline was positively predictive of subsequent per cent change in HAM-D, in the full model and individually (r=0.406, *p*=0.019, collapsing across active (magenta) and sham (cyan) conditions). There was no interaction with stimulation group (F(1,29)=0.544, *p*=0.469).

6.4.3.1 Sensitivity analysis: right amygdala (fearful>neutral contrast)

To test the sensitivity of the right amygdala model, we iteratively tested for multicollinearity between all independent variables. The variance inflation factor (VIF) did not exceed our threshold of 3 (all VIF<1.5). Therefore, the initial model included all six variables, as well as interactions with stimulation group. The overall model was non-significant ($F(11,29)=0.93$, $p=0.532$); therefore, we did not continue with backwards elimination. However, in the initial model, right amygdala activation remained a significant predictor of outcome ($F(1,29)=6.52$, $p=0.019$) (all other predictors and their interactions with stimulation group were not, $p>0.2$).

6.4.3.2 Reliability analysis: right amygdala (fearful>neutral contrast)

We next calculated the within-subject reliability of right amygdala activation to fearful faces. The right amygdala showed poor reliability between scans: ICC=-1.630,

95%CI=-4.325– -0.299, *p*=0.996. This did not differ between the groups (active: ICC=-1.83, 95%CI=-6.35– -0.09, *p*=0.984. sham: ICC=-1.26, 95%CI=-6.04– -0.27, *p*=0.923) (see Figure 6.3B).

6.4.4 Right DLPFC model

In a model containing only right DLPFC activation and stimulation group, right DLPFC activation did not predict percent change HAM-D, either alone (*F*(1,29)=1.05, *p*=0.314), or interacting with stimulation group (*F*(1,29)=0.46, *p*=0.503). Therefore, we did not continue with sensitivity or reliability analyses.

6.4.5 Left amygdala model (happy>neutral contrast)

In a model containing only left amygdala activation (happy>neutral contrast), left amygdala activation did not predict percent change HAM-D, either alone (*F*(1,29)=0.18, *p*=0.676), or interacting with stimulation group (*F*(1,29)=0.72, *p*=0.405). Therefore, we did not continue with sensitivity or reliability analyses.

6.4.6 Right amygdala model (happy>neutral contrast)

In a model containing only right amygdala activation (happy>neutral contrast), right amygdala activation did not predict percent change HAM-D, either alone (*F*(1,29)=0.73, *p*=0.399), or interacting with stimulation group (*F*(1,29)=0.007, *p*=0.935). Therefore, we did not continue with sensitivity or reliability analyses.

6.4.7 sgACC model (fearful>neutral contrast)

In a model containing only sgACC activation (fearful>neutral contrast), sgACC activation did not predict percent change HAM-D, either alone (*F*(1,29)=1.12,

p=0.299), or interacting with stimulation group (*F*(1,29)=1.62, *p*=0.214). Therefore, we did not continue with sensitivity or reliability analyses.

6.4.8 sgACC model (happy>neutral contrast)

In a model containing only sgACC activation (happy>neutral contrast), sgACC activation did not predict percent change HAM-D, either alone (*F*(1,29)=0.52, *p*=0.475), or interacting with stimulation group (*F*(1,29)=0.60, *p*=0.444). Therefore, we did not continue with sensitivity or reliability analyses.

6.4.9 Exploratory whole brain analyses: n-back task

A whole-brain analysis examining potential predictors of response from baseline n-back task activation (implemented as an independent samples *t*-test with percent change in HAM-D as a covariate) revealed only one cluster significantly associated with the degree of response. This was the case collapsing across both groups, and examining the interaction with stimulation group, at whole-brain level as well as using small-volume correction in the left and right DLPFC (no clusters survived a threshold of *p*<0.001 (uncorrected) after SVC). Activation in the posterior parietal cortex (PPC, k=69) was significantly associated with symptom reduction (*p*=0.027, FWE cluster-corrected) (see Figure 6.5). See Table 6.1 for full results (*p*<0.001 (uncorrected), minimum cluster size k=4).

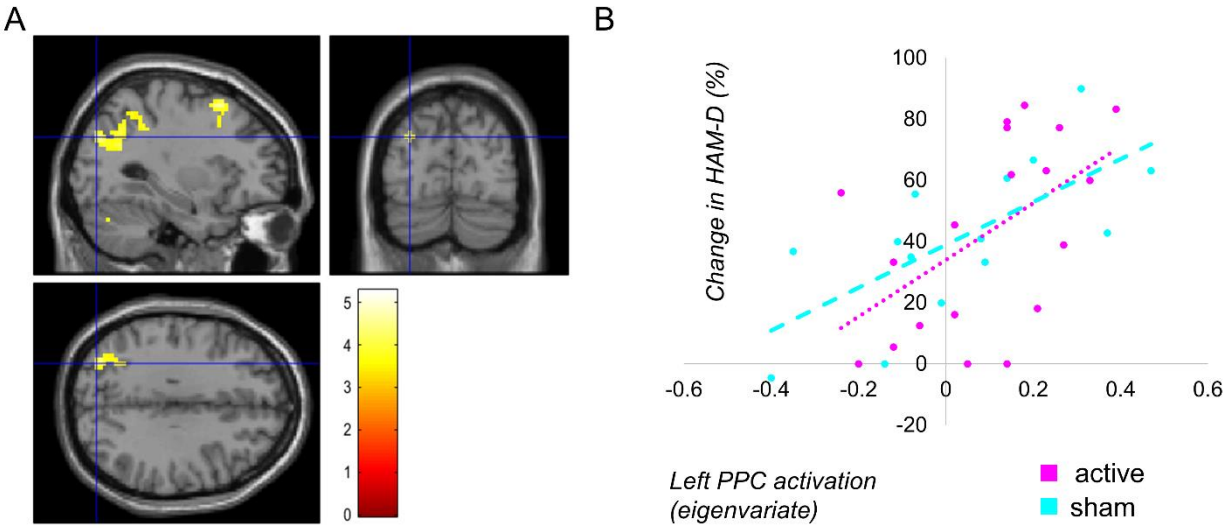

Figure 6.5 Association between Left PPC and mood improvement. A. Results of whole-brain exploratory analysis for regions predictive of outcome in the n-back task (3-back>1-back contrast) (p<0.001 uncorrected, minimum cluster size k=4). Crosshairs located at peak voxel in left posterior parietal cortex (L PPC). B. Relationship between L PPC activation (eigenvariate of cluster) and percent reduction in Hamilton Depression Rating Scale (HAM-D) over the trial (p=0.027, cluster-corrected) in active (magenta) and sham (cyan) groups.

Effect (all contrasts 3-back > 1-back)	*p* (cluster-corrected)	Extent	*p* (voxel-corrected)	t(29)	Z	Y	Z	region
Response (both)	0.118	43	0.143	5.26	6	-22	-4	L thalamus
	0.074	51	0.451	4.64	-30	14	56	L premotor
	0.158	38	0.580	4.47	24	20	53	R premotor
	0.027	69	0.633	4.40	-30	-79	32	L PPC
	0.132	41	0.755	4.24	-27	-46	41	L parietal
	0.791	10	0.814	4.15	-15	-61	26	L posterior cingulate
	0.912	6	0.847	4.10	-33	-70	-31	L cerebellum
	0.824	9	0.932	3.92	-48	-52	11	L PPC
	0.957	4	0.962	3.82	18	11	8	R caudate
Nonresponse (both)	none							
Sham>active	0.688	13	0.320	4.85	-3	-16	2	L thalamus
	0.937	5	0.719	4.29	12	-40	-10	R cerebellum
	0.791	10	0.908	3.98	-27	-19	59	L premotor
	0.937	5	0.966	3.80	-9	2	47	L SMA
Active>sham	none							

Table 6.1 N-back task: whole-brain correlates of response. Whole-brain correlates of response for n-back task (cluster-forming threshold $p<0.001$, (uncorrected); minimum cluster size=4). R=right; L=left; PPC=posterior parietal cortex; SMA=supplementary motor area.

6.4.10 Exploratory whole brain analyses: emotional faces task (fearful>neutral contrast)

We repeated this exploratory analysis for baseline emotion processing activation, using the fearful>neutral faces contrast (whole-brain analysis: independent samples t-test with covariate percent change in HAM-D). Here, we found a cluster in the rostral PFC and orbitofrontal cortex (OFC) in which stronger activation was associated with a greater improvement in HAM-D across both stimulation groups (p=0.001, cluster-corrected) (see Figure 6.6). We did not find any other clusters positively or negatively associated with the degree of symptom improvement, either across both groups, or examining the interaction with stimulation group (sham>active and active>sham), at whole-brain level or using small-volume correction in our three ROIs (sgACC and amygdalae) (no clusters below $p<0.001$ (uncorrected) after any of

the SVCs). See Table 6.2 for full results (p<0.001 (uncorrected), minimum cluster size k=4).

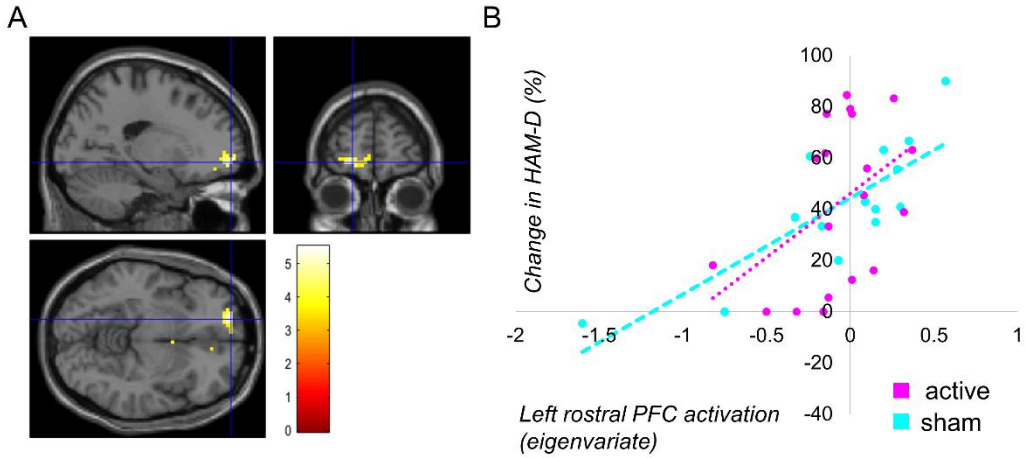

Figure 6.6 Association between left rostral PFC and mood improvement. A. Results of whole-brain exploratory analysis for regions predictive of outcome in the emotion processing task (fearful>neutral contrast) (p<0.001 uncorrected, minimum cluster size k=4). Crosshairs located at peak voxel in left rostral prefrontal cortex (PFC); activation extends into bilateral OFC. B. Relationship between left rostral PFC activation (eigenvariate of cluster) and percent reduction in Hamilton Depression Rating Scale (HAM-D) over the trial (p=0.001, cluster-corrected) in active (magenta) and sham (cyan) groups.

Effect (fearful> neutral)	p (cluster-corrected)	Extent	p (voxel-corrected)	t(29)	Z	Y	Z	region
Response (both)	0.001	121	0.110	5.49	-18	59	-7	L rostral PFC
	0.966	4	0.932	4.04	-21	-16	-1	L GP
	0.678	12	0.933	4.04	12	-82	-28	L cerebellum
	0.845	8	0.945	4.01	6	-4	-16	R hypothalamus
	0.915	6	0.982	3.84	27	-61	-37	R cerebellum
	0.915	6	0.993	3.73	60	-16	-25	R temporal
Non-response (both)								
Sham>active	0.882	7	0.383	4.86	6	-25	-10	R substantia nigra
	0.915	6	0.730	4.39	-9	17	11	L caudate
	0.882	7	0.946	4.00	3	5	8	R thalamus
	0.678	12	0.994	3.72	6	47	-10	R rostral PFC
	0.966	4	0.999	3.55	-3	44	-22	L VMPFC
Active>sham	none							

Table 6.2 Whole-brain correlates of response (fearful>neutral). Whole-brain correlates of response for emotion processing task (cluster-forming threshold p<0.001 (uncorrected); minimum cluster size=4). R=right; L=left; PFC=prefrontal cortex; VMPFC=ventromedial prefrontal cortex; GP=globus pallidus.

6.4.11 Exploratory whole brain analyses: emotional faces task (happy>neutral contrast)

We again conducted an exploratory analysis examining potential predictors of response (percent change in HAM-D) from the baseline emotion processing scan, using the happy>neutral faces contrast (whole-brain analysis: independent samples t-test with covariate per cent change in HAM-D). Here, we did not find any significant clusters positively or negatively associated with the degree of response, collapsing across both groups or examining the interaction with stimulation group, either at whole-brain level or using small-volume correction in our three ROIs (sgACC and amygdalae: no clusters $p<0.001$ uncorrected for the any SVC). See Table 6.3 for full results ($p<0.001$, minimum cluster size k=4).

Effect (all contrasts happy > neutral)	p (cluster-corrected)	Extent	p (voxel-corrected)	t(29)	X	Y	Z	region
Response (both)	0.526	16	0.872	4.16	-18	5	29	Cingulate gyrus
	0.882	7	0.954	3.96	6	2	-7	BNST
Non-response (both)	.915	6	0.805	4.27	-24	2	5	L putamen
Sham>active	none							
Active>sham	0.767	19	0.812	4.26	24	32	-4	Basal operculum

Table 6.3 Whole-brain correlates of response (happy>neutral). Whole-brain correlates of response for the happy>neutral faces contrast in the emotion processing task (cluster-forming threshold $p<0.001$, uncorrected; minimum cluster size=4). BNST=bed nucleus of the stria terminalis.

6.5 Discussion

We conducted an analysis of potential predictors of clinical response to tDCS and CBT. We identified an fMRI measurement that specifically predicted response to active relative to sham tDCS for depression when combined with CBT: left DLPFC activation during working memory processing. We also report three general predictors of treatment response in our trial, which potentially indicate likelihood of response to CBT irrespective of stimulation: right amygdala activation (in line with previous reports (Siegle et al., 2006, 2007a)) and rostral PFC activation, both during fearful face processing; and left PPC activation during the n-back task. Left DLPFC activation, but not right amygdala activation, showed high within-subject reliability between the two scan dates, supporting its potential use as a predictor of treatment response.

6.5.1 The left DLPFC as a predictor of response for antidepressant tDCS

We predicted *a priori* that the left DLPFC (for tDCS) and the amygdalae (for CBT in general) might be associated with clinical outcome. We revealed a strong positive association between greater baseline left DLPFC activation during working memory (3-back>1-back contrast) and clinical outcome in the trial (measured as percent decrease in HAM-D score). Crucially, in both models (i.e., the single-predictor model and the sensitivity analysis), left DLPFC activation interacted with stimulation group, indicating differential associations with clinical outcome between the groups. Splitting by group, the left DLPFC strongly predicted clinical outcome in the group receiving active tDCS; this was not the case in the sham group. Thus, we show specificity for this predictor for our combined tDCS/CBT intervention.

The left DLPFC finding represents one of the first fMRI 'biomarkers' of tDCS response (as far as we are aware, the first for depression). It follows more tentative recent findings that spectral power in frontal scalp channels can classify clinical response to tDCS with above chance accuracy using a machine learning algorithm (Al-Kaysi et al., 2017). Additionally, one study has shown clinical response to left DLPFC TMS is associated with baseline perfusion in the left DLPFC (Weiduschat & Dubin, 2013) (though this finding is not consistent across studies (Kito et al., 2008, 2012)).

The DLPFC has rarely been suggested as a predictor of treatment response in psychiatry, but our results suggest it may hold particular potential in predicting response to neurostimulation to this area in depression, at least in the case of tDCS with CBT. One useful feature of activation in DLPFC during n-back performance is its relatively strong within-subject reliability, which is an important criterion for a clinically useful predictor. This suggests the BOLD response in the left DLPFC during working memory processing is more stable than regions such as the sgACC and amygdalae during emotion processing, which are often proposed as 'biomarkers' but have been reported to have very low within-subject reliability (Nord et al., 2017a). This finding was replicated in our analyses of the right amygdala in this chapter.

It may be important that a specific predictor of clinical response to tDCS was found during the task performed concurrently with tDCS delivery during the intervention (see Chapter 5 for details). The acute effects of tDCS on behaviour are known to be dependent on the state of the specific network targeted: theoretically, the electrical current causes firing specifically in the neurons closest to depolarization (Tremblay et al., 2014). This "state-dependency" of tDCS has been suggested as one factor

mediating the inter-individual differences in susceptibility to tDCS effects. It is possible that our relatively low level of current (1 mA) was only sufficient to evoke clinical changes in patients with already-strong activity in that region during the n-back task at baseline. Possibly, patients with lower baseline activity may require a greater tDCS current to produce an antidepressant effect, though this needs to be confirmed in future studies. This could be one explanation for the association between greater current levels and antidepressant efficacy reported in a meta-analysis (Brunoni et al., 2016). Baseline DLPFC activation might index the relative sensitivity of the cortex to tDCS, and could in future be used to adjust dose. This prospect would be very interesting to investigate in future studies: at the moment, rTMS dose for depression is adjusted according to local physiology (i.e., motor evoked potentials) (George et al., 2000), yet tDCS dose is usually delivered identically across all patients.

Our sensitivity analyses showed that baseline activation in the left DLPFC predicts clinical outcome, even after accounting for other possible predictors. For instance, n-back performance (d') was not a significant predictor of response, implying that the association between left DLPFC activation and clinical response does not appear to be a proxy for a relationship between better working memory and clinical outcome. Additionally, the symptom measures associated with clinical response in the left DLPFC model (baseline depression and anxiety symptoms) were not associated with clinical response when examined independently outside the full regression. Therefore, baseline left DLPFC activation seems to provide useful information about clinical outcome, over and above other characteristics.

6.5.2 The right amygdala as a possible predictor of response to CBT

Our right amygdala (fearful>neutral contrast) single-predictor model was also significantly associated with clinical outcome. In contrast to the left DLPFC, this association did not differ between the groups. This suggests that clinical response to tDCS is not mediated by baseline activation in the amygdala, but that response to CBT may be. This replicates two previous reports that greater baseline amygdala activation during negative information processing predicts improvement following a course of CBT (Siegle et al., 2006, 2007a). However, our results also replicate recent findings that amygdala activation to emotional faces has very poor within-subject reliability, which would indicate it has less use as a potential predictor of treatment response (Nord et al., 2017a). What might explain this discrepancy?

Our finding of unreliable amygdala activation during fearful face processing could be interpreted in several ways. It could simply indicate noise in the region measured, the amygdala. Alternatively, amygdala activity itself might be perfectly stable, but our measurement tool (fMRI) or its measure (the BOLD response) might not be. In either of these cases, the amygdala would show poor within-subject reliability in fMRI studies, as we have shown (Nord et al., 2017a). However, if this were the case, one would also expect the association between amygdala activation and treatment response to show poor replicability. Since our results replicated two previous associations between amygdala activation and treatment response (Siegle et al., 2006, 2007a), this seems somewhat contradictory. For this reason, it is worth considering another possible explanation. Potentially, the initial exposure to emotional faces evokes specific amygdala activation (e.g., amygdala ‘reactivity’) that is not evoked by future runs, but is itself a reliable predictor of treatment-

responsiveness. If this were the case, separate groups of individuals might all show such an association, but the individuals themselves would not necessarily show reliable responses when scanned on multiple occasions. If this were the case, we would predict that a second run of the task at baseline (which we have previously shown is not associated with activation in the first run (Nord et al., 2017a)) would not be associated with treatment response, and we would recommend future studies not to collapse across two runs to examine associations with clinical outcome variables. However, as we only included a single run of emotional face processing in our scanning session, we cannot test this proposal.

6.5.3 Other ROI analyses and exploratory whole-brain results

The remaining single-predictor ROI analyses did not reveal any other outcome predictors: the right DLPFC (to 3-back>1-back), right amygdala (to happy>neutral faces), left amygdala (to fearful and happy>neutral faces), and sgACC (to fearful and happy>neutral faces) were not associated with clinical outcome. Exploratory whole-brain analyses for the happy>neutral contrast of the emotion processing task also did not show an association between any regions and clinical response, either overall or interacting with group.

However, exporatory whole-brain analysis of the n-back task (3-back>1-back contrast) showed a large cluster in the posterior parietal cortex associated with symptom reduction across both groups. This suggests patients with greater posterior parietal activation during working memory are more responsive to CBT (or perhaps to treatment in general). The parietal cortex forms an essential component of the verbal working memory network activated in the n-back task in both healthy controls and depressed patients (Harvey et al., 2005), including in the present study (Chapter

4). Several studies have reported increased parietal cortex metabolism after CBT (though both used PET, not fMRI) (Goldapple et al., 2004; Kennedy et al., 2007). Given the involvement of the parietal cortex in both working memory and CBT, it is plausible that baseline PPC activation could be associated with a patient's likelihood of responding to CBT. However, from our trial design we cannot distinguish between predictors of response to CBT specifically and predictors of any other intervention (including placebo); therefore, it is possible that PPC activation is also simply a non-specific predictor of response to treatment in general.

Another general predictor of treatment response was found in the whole-brain analyses of the emotion processing task (fearful>neutral contrast), which showed a cluster of activation associated with clinical outcome across both groups in the anterior PFC, with the peak in the right rostral PFC, extending into bilateral OFC. This suggests that patients with greater activation in this region at baseline are more responsive to CBT (or potentially to treatment in general). In a previous study, activation in the vmPFC/OFC was associated with greater symptom improvement from CBT (however, the contrast used was all pictures (negative, positive, and neutral) versus baseline; i.e. this result was not found for negative stimuli specifically) (Ritchey et al., 2011). Additionally, a prominent theory suggests the rostral PFC functions as a 'supervisory attentional gateway', enabling attention to be directed toward either external environmental stimuli or internal mental representations (Burgess et al., 2007). This function, in combination with the role of the OFC in top-down control of negative emotion (Agustín-Pavón et al., 2012) may be crucial for successful engagement with CBT. In particular, this might help patients learn to disengage from internal ruminative thinking patterns, and re-direct attention toward pragmatic (external) goals.

6.5.4 Limitations and future directions

Our results should be interpreted with several caveats. Our findings lead us to propose the left DLPFC as a novel predictor of response to tDCS/CBT in depression. However, since our trial combined tDCS with CBT for depression and no group received tDCS without CBT, it is not clear whether this would generalise to tDCS treatment alone. Therefore, future studies should test whether this replicates in a sample treated only with tDCS. Additionally, our findings may not extend to tDCS interventions with different parameters (including different montages, stimulation intensities, and delivery protocols). It also bears mentioning that the association between amygdala activation and response to CBT was found only in the right amygdala, and that the right amygdala showed very poor within-subject reliability, unlike the left DLPFC. On its own, this would not support the amygdala as a potential predictor of response to CBT response. However, given this finding replicates previous results (Siegle et al., 2006, 2007a), and particularly if it is replicated again in future, the amygdala could represent a predictor for CBT response (or possibly response generally). Finally, while our sample (N=33) represents one of the larger trials of tDCS in depression, it is almost certainly underpowered to detect more subtle associations, which might become apparent with a larger sample size.

6.5.5 Conclusion

This study begins to clarify the common and distinct mechanisms involved in response to interventions in depression. Our results raise the possibility of a novel predictor of response to tDCS in depression, left DLPFC activation during working memory, which appears to be relatively strong and specific. In the n-back task, we also found a relationship between increased baseline left PPC activation and better

response to CBT. We also found an association between greater right amygdala activation and rostral PFC/OFC activation during fearful face processing and better response to CBT, replicating and extending a small number of previous findings implicating the amygdala and ventral PFC in CBT (Ritchey et al., 2011; Siegle et al., 2006, 2007a). More generally, our findings provide evidence that neuroimaging techniques can provide valuable information when included in RCTs, not only illuminating the neural changes associated with treatments, but also identifying measurements that may eventually guide treatment selection in psychiatry.

Chapter 7: General discussion

This general discussion chapter will begin by summarising the experimental findings presented in this thesis. It will then integrate the findings of the experimental chapters, discussing the possible role of DLPFC dysfunction in depression, and whether tDCS targets cold cognitive mechanisms involved in generating depressive symptoms, as proposed by the cognitive neuropsychological model. It will also briefly discuss the less-clear role (at least in the work presented in this thesis) for hot cognitive mechanisms in the effects of DLPFC tDCS. Lastly, it will discuss how (and whether) these findings could inform clinical treatment in depression, examine the limitations of the studies presented in the thesis, and suggest some techniques to refine the approach of DLPFC tDCS clinical trials in the future.

7.1 Summary of chapters

Chapter 3

In Chapter 3, I aimed to test whether anodal tDCS of the DLPFC (the montage used in depression trials) acutely modulated a measure of low-level hot cognitive processing, facial emotion identification. tDCS did not show an emotion-dependent effect on behaviour. Instead, anodal tDCS substantially slowed reaction times across all emotions. In a subset of participants, we found that the degree to which participants were slowed by tDCS (relative to sham) was related to their distractibility during active stimulation. These findings suggest that tDCS does not modulate low-level hot cognition, unlike many antidepressant drugs, which acutely shift emotion identification towards positive emotions (Harmer et al., 2003b, 2009b). Rather, we

speculated that tDCS may improve mood via effects on cold cognitive processes associated with depression.

Chapter 4

tDCS purportedly targets dysfunctional DLPFC activation in depression, but the directionality of this dysfunction, and its role in risk and resilience for depression, remains unclear. In Chapter 4, I measured the extent and direction of DLPFC dysfunction in an fMRI paradigm using the working memory n-back task, comparing patients with unipolar depression to matched healthy controls and a group of at-risk unaffected first-degree relatives. I also measured sgACC and amygdala activation during hot cognitive processing using an incidental emotion processing task. Together, these paradigms tested an important prediction of the cognitive neuropsychological model: that biased hot cognition confers risk for depression, while preserved cold cognitive processing might mitigate this risk.

I found that depressed patients showed blunted DLPFC responses during working memory processing (contrast: 3-back>1-back) compared to healthy controls. In contrast, at-risk relatives showed intact DLPFC activation, indistinguishable from healthy controls. However, I did not find a complementary pattern in sgACC or amygdala response to emotion processing. I found a preliminary relationship between amygdala activation during happy (but not fearful) emotion processing and DLPFC activation during working memory processing across all three groups: individuals with lower DLPFC activation showed higher amygdala activation, consistent with the notion that the DLPFC may play a role in downregulating amygdala activation in both healthy and depressed states. Thus, the pattern of results only partially confirmed our prediction, finding preserved DLPFC activation in

at-risk relatives, suggesting that the DLPFC may play a role in promoting resilience against risk for depression. However, the idea that this risk is associated with amygdala responses to negative stimuli was not supported. This finding could also support potentially targeting dysfunctional DLPFC activity in the treatment of depression, a notion I tested in Chapter 5.

Chapter 5

I conducted a double-blind RCT to test whether tDCS enhanced the effects of CBT for depression in Chapter 5. Unmedicated patients with unipolar depression received eight weekly sessions of CBT, immediately preceded by 20 minutes of either active or sham tDCS. Patients received two fMRI scans, before and after the intervention, measuring neural activation during hot and cold cognitive processing. Active tDCS did not have a significant effect on response (odds ratio: 2.16, p=0.12) and remission (odds ratio: 3.65, p=0.066) rates, compared to sham. There were also no significant differences in weekly working memory performance between active and sham conditions. There was a substantial increase in DLPFC activation (during working memory: 3-back vs 1-back) following the CBT intervention, but this was the case across both treatment arms. By contrast, amygdala and left DLPFC activation during emotion processing differed between the groups at the end of the trial: both generally decreased over the course of the study in patients receiving sham, but not in patients receiving active stimulation. These results inform our mechanistic understanding of tDCS, but do not support a benefit of active over sham stimulation on depressive symptoms. However, this result may be driven by variability in response to both tDCS and to psychotherapeutic interventions in general. I tested this notion in Chapter 6.

Chapter 6

Chapter 6 investigated whether baseline neural responses could predict clinical outcome following the tDCS/CBT intervention. I showed that activation at baseline in the left DLPFC specifically predicted mood improvement following active, but not sham stimulation. I also found that baseline right amygdala activation during emotion processing predicted outcome irrespective of stimulation group. This confirms previous reports that baseline amygdala activation could predict general treatment response in depression (Siegle et al., 2006, 2007a). Finally, I conducted a whole-brain exploratory analysis which identified two regions surviving correction for multiple comparisons, the left rostral PFC (during emotion processing) and left posterior parietal cortex (during working memory); greater activation in both of these regions predicted better response to CBT across both stimulation arms. In summary, this chapter identified several regions that may be useful in predicting treatment response. In particular, the left DLPFC may represent the first putative fMRI 'biomarker' of treatment response to tDCS in depression.

7.2 Are cold cognitive mechanisms a putative treatment target in depression?

Much of this thesis draws on the hypothesis that cold cognitive deficits and their neural correlates are central to the development of depressive symptoms, and that targeting these processes might be helpful in the treatment of depression. We focused on one such neural correlate of cold cognition in particular: DLPFC activation during the n-back working memory task, specifically, how the DLPFC contributes to risk for depression (Chapter 4), whether stimulating the DLPFC would ameliorate depressive symptoms (Chapter 5), and whether DLPFC activation could

predict clinical response (Chapter 6). These predictions were derived in part from the cognitive neuropsychological model of depression, in which DLPFC dysfunction is proposed to underlie certain symptoms of depression, including diminished cognitive control (Roiser and Sahakian, 2013).

7.2.1 DLPFC in depression: hypo- or hyperactivity?

There is substantial evidence to support the existence of DLPFC abnormalities in depression (Baxter et al., 1989; Bench et al., 1993; Fales et al., 2009; Harvey et al., 2005; Siegle et al., 2007a). However, it is unclear why functional imaging studies during cold cognitive tasks, most commonly the n-back, sometimes report excessive activation of the DLPFC in depression (Harvey et al., 2005), while others find lower activation, as in our patient group (Chapter 4) and previous reports (Elliott et al., 1997a).

Previous studies have explained this discrepancy as an example of imperfect matching of behavioural performance between patients and controls. According to this explanation, when patients are behaviourally impaired, they will appear "hypofrontal", compared to healthy controls; when patients and controls are behaviourally matched, patients will show hyperfrontality (Harvey et al., 2005). This is supported by a meta-analysis finding that when behaviour is matched, patients show DLPFC hyperactivation during the n-back task (Wang et al., 2015). This scenario – when groups are matched for working memory performance – was treated as the optimal context to measure group differences in DLPFC activation in this meta-analysis. However, it is not clear that 'behavioural matching' is truly optimal for an fMRI study. If patients are impaired at a particular cognitive function relevant to the phenomenology of depression (for example, if they show a 'catastrophic'

response to perceived failure (Elliott et al., 1997b)), matching the behavioural performance of patients with controls before drawing conclusions about the neural mechanisms might mask the mechanisms underpinning the very behaviours thought to be abnormal in the first place (Murray et al., 2010). Indeed, even if performance was matched, most researchers would assume that any neural differences affected task-relevant behaviours.

In our study (Chapter 4), we did not detect a significant main effect of group on behavioural performance in the 3-group ANOVA (p=0.149), and so did not perform post-hoc analysis. However, patients did perform numerically worse than controls (controls: M=2.03 SD=0.93; patients: M=1.56, SD=0.87; Cohen's d=0.52). However, it should be noted that we had limited power (approximately 70%) to detect a difference between groups in working memory performance on the order of d~0.6, as reported in meta-analyses (Snyder, 2013), which complicates the interpretation of this non-significant result. In summary, while our finding of DLPFC hypoactivation could fit with the explanation of imperfect group matching on behavioural performance, the study was underpowered to support this explanation unequivocally.

7.2.2 Inverted U-shaped curve hypothesis of DLPFC activity

A similar association between behavioural performance and the direction of group differences appears in the schizophrenia literature (Callicott et al., 2003). In schizophrenia, there is evidence that patients with poor n-back performance show hypofrontality during the n-back task, but as performance approaches the level of healthy controls, hyperfrontality emerges (Manoach, 2003). Callicott and colleagues proposed that the relationship between increasing working memory load and DLPFC activation followed an inverted U-shaped curve, which is shifted in schizophrenia

(Callicott et al., 2003). In this model, very low load working memory tasks are insufficient to activate the DLPFC; moderately high load tasks evoke peak DLPFC activation; and high load tasks that exceed working memory capacity no longer activate the DLPFC. In schizophrenia, the model posits that a shifted inverted U-shaped curve results in patients appearing hypofrontal under easier working memory load conditions, but hypofrontal under more difficult conditions (in other words, patients exceed working memory capacity sooner). In a similar manner, such an explanation could also account for the discrepancies in group differences in depression (see Figure 7.1).

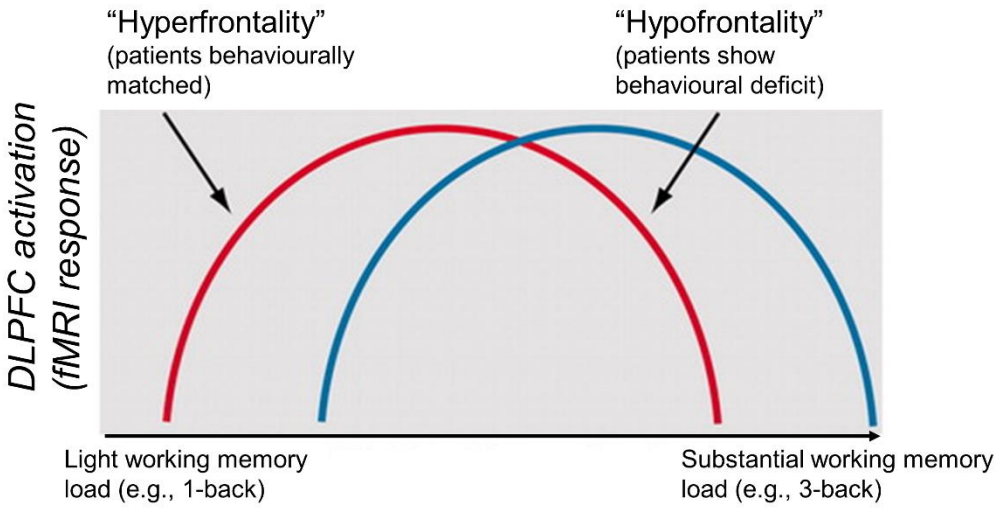

Figure 7.1 Suggested inverted U-shaped relationship between DLPFC activation during n-back task and working memory load in depression. Figure adapted from its prosed role in schizophrenia (Callicott et al., 2003). This model is characterized by a shifted inverted U-shape load-response curve in depressed patients, which accounts for hypofrontality reported in Chapter 4 (and elsewhere) in depressed patients (right side of the figure: when working memory load exceeds capacity more in patients than controls, the DLPFC appears underactive) and hyperfrontality reported in previous studies (left side of the figure: when low working memory load is closer to peak capacity in patients than controls).

In depression, studies with matched behaviour between patients and controls might sample from the left side of these inverted U-shaped curves (for instance by using an easier task, such as the 2-back), and therefore find DLPFC hyperactivation in patients (see Figure 7.1). By contrast, where patients are impaired on the n-back

task (or slightly impaired, like ours), group differences in DLPFC activation would resemble the right side of the curve (hypofrontality), when working memory has exceeded patients', but not controls', working memory capacity.

This might also explain the pattern observed in Chapter 5: post-intervention, patients showed increased DLPFC activation in both trial arms, which was statistically indistinguishable from the healthy control sample in Chapter 3 (post-intervention patients: M=2.24, SD=0.93; controls: M=2.03, SD=0.93). In patients, n-back performance improved substantially over the course of the trial. Possibly, repeated practice of the task made the difficult 3-back condition easier for patients, such that it no longer exceeding working memory capacity (in Figure 7.1, this would be equivalent to moving towards the left side of the curve). However, one caveat to this explanation is that we did not observe an association between n-back task improvement and change in DLPFC activation. One might predict that if we had repeatedly tested healthy volunteers on the n-back such that they also showed performance improvements, they may have shown decreased DLPFC activation after repeated practice, such that patients would then appear hyperactive. This hypothesis is consistent with studies showing decreases in DLPFC activation (in healthy controls) after practicing a working memory task (Garavan et al., 2000), but it remains to be tested in depressed patients.

The subsequent chapters (5 and 6) explore whether dysfunctional DLPFC activation in depression (potentially represented as a shifted inverted U-curve) could be targeted directly with tDCS to harness resilience mechanisms and ameliorate symptoms.

7.3 Does tDCS affect cold cognitive mechanisms?

Although in Chapter 3 we initially predicted tDCS would produce acute effects on low-level hot cognition, we found that tDCS had emotion-independent effects. This suggested that tDCS might instead acutely modulate cold cognition. This was supported by previous findings that tDCS acutely affected other cold cognitive processes, most notably working memory, in both healthy controls and depressed patients (Lally et al., 2013; Oliveira et al., 2013). In the context of the cognitive neuropsychological model of depression, tDCS is posited to increase cognitive control, and by extension engagement with CBT and reality-monitoring in general: its hypothesized role is depicted in Figure 2.

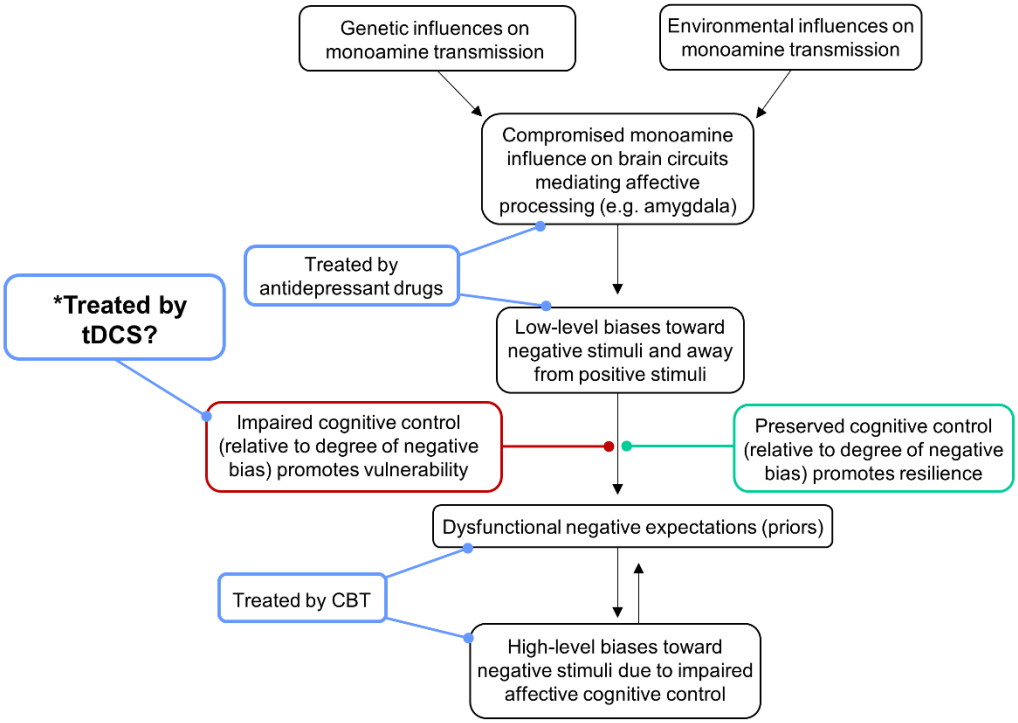

Figure 7.2. The cognitive neuropsychological model of depression. Primary hypothesis for the role of tDCS on cognitive control indicated with an asterisk (*). Figure adapted from (Roiser et al., 2012).

7.3.1 Null effect of tDCS on behavioural measures of cold cognition

However, these hypothesized effects of tDCS on cold cognition (working memory) were not borne out in Chapter 5: we showed no effect of stimulation group on working memory performance over the eight trial sessions. Recent work has also failed to show an additive effect of multiple stimulation sessions on n-back performance in healthy volunteers (Talsma et al., 2017), consistent with our findings. Therefore, the cognitive mechanisms underlying any potential antidepressant effects of tDCS cannot be explained by a substantial improvement in cold cognitive function, at least not as measured by the n-back. Furthermore, we did not detect a significant effect of DLPFC tDCS (plus CBT) on depression symptoms themselves, relative to sham stimulation plus CBT (discussed in more detail in section 7.5). It is possible that with a larger sample size, we might have had the power to detect an effect on depression scores. However, it is unlikely that a lack of power alone can explain our null result on n-back working memory performance, particularly because the sham tDCS group showed a significantly greater improvement in working memory performance measured inside the scanner (from pre- to post-intervention) than the active tDCS group.

There were no group differences in behavioural performance outside the scanner; crucially, in the tDCS literature, the in-scanner performance is classified as an "offline" tDCS protocol measure (i.e., a measure assessed after, rather than during, stimulation), while performance outside the scanner was always measured during tDCS delivery ("online"). Within the context of the trial, this result might imply that CBT (or simply practice on the task) simply improves n-back task performance, but that this improvement is lessened under anodal tDCS. A deleterious effect of anodal

tDCS of the DLPFC on offline working memory performance has not been reported to our knowledge, but could be a cautionary tale for research on tDCS as a putative 'cognitive enhancer'. Interestingly, the possibility that tDCS could exert a deleterious effect is not incompatible with our results from Chapter 3, which showed substantially slower reaction times to identify emotions under anodal tDCS (however, we also found that tDCS improves accuracy on the distraction task, which is more consistent with typical 'enhancement' reports).

It bears mentioning that in Chapter 5 we found a large difference between active and sham conditions on one adverse effect, trouble concentrating: patients receiving sham stimulation reported substantially (~60%) more instances of trouble concentrating than those receiving active stimulation (X^2=22.26, p<0.001) (this effect was in the same direction in Chapter 3). It seems unlikely that this is an adverse effect of sham stimulation, which involves very low amounts of stimulation (30 seconds ramping to 1 mA at the beginning, then no stimulation for the rest of the 20 minutes). Rather, this could imply that active tDCS improves concentration. This certainly fits with studies reporting effects of tDCS on attention, learning, and memory (Coffman et al., 2014). However, it does not fit with the lack of effect of tDCS on n-back performance in our study. It is possible tDCS improves subjective feelings of concentration, even in the absence of behavioural enhacements. Still, our results suggest that the effect of tDCS on concentration should be investigated explicitly in future, potentially using both a cognitive task that directly measures concentration, as well as self-report measures of concentration.

7.3.2 Effect of tDCS and CBT on neural measures of cold cognition

While we did not show specific effects of tDCS on cold cognitive performance or related activation in the DLPFC, we did show a general effect of our intervention (or practice on the task) on DLPFC activation, irrespective of stimulation group. Thus, some aspect of the intervention (or practice on the task) did target DLPFC hypoactivation: patients were statistically indistinguishable from healthy controls (and first-degree relatives) after the intervention. In addition to practice effects on the n-back task, which could increase DLPFC activation by decreasing the difficulty of the n-back task (i.e., moving left in the direction of peak activation on the inverted U-curve), CBT itself may also have increased DLPFC activation in both active and sham stimulation groups. This would be consistent with the suggestion that CBT remediates pre-treatment DLPFC hypoactivation (DeRubeis et al., 2008).

This finding was qualified by our result from Chapter 6, where we showed that higher baseline activation in the left DLPFC pre-intervention specifically predicted response to active, but not sham, tDCS. Thus, cold cognitive function (as putatively measured by left DLPFC activation during the n-back task) seems to relate specifically to the mechanism of tDCS, which broadly supports our conclusions from Chapter 3, and perhaps indicates that these patients show a degree of resilience (in-line with Chapter 4), but that this resilience was only harnessed through tDCS and CBT in combination, not by CBT alone. A caveat to this explanation is that cold cognitive function as assessed by the n-back task did not predict clinical outcome (in general, or to tDCS specifically). It is possible that this relationship would emerge in a larger sample (i.e., the DLPFC-outcome relationship may simply have a larger effect size, and therefore be easier to detect in a small sample such as ours). It is also possible

that DLPFC activation during the n-back task is reflective of a more general cold cognitive capacity than working memory ability *per se*; other measures of executive function (or perhaps a combined measure) may be better predictors of outcome than the n-back.

7.4 Does DLPFC tDCS also affect hot cognitive mechanisms?

Few previous studies have investigated the effect of DLPFC tDCS on hot cognitive processing. Chapter 3 provided strong evidence that tDCS did not modulate emotion identification, one important measure of low-level hot cognitive processing. However, emotion identification is only one measure of hot cognition, and it is certainly possible there are other aspects of hot cognition affected by tDCS. This possibility is supported by two previous studies (Ironside et al., 2015; Vanderhasselt et al., 2013); in the RCT, we also found tentative evidence for the involvement of hot cognitive mechanisms in the neural effects of multiple-session tDCS (Chapter 5).

7.4.1 Effect of tDCS on behavioural measures of hot cognition

In Chapter 3, an important limitation of our task was its measurement of purely low-level hot cognitive processing (i.e., perceptual biases). Although we find evidence against acute effects of tDCS on these measures, it is possible that DLPFC tDCS has an effect on other measures of hot cognition not measured by this task. In support of this, a previous study found tDCS acutely improved inhibition of habitual responses to happy compared to sad facial expressions (Vanderhasselt et al., 2013). Thus, acute effects of tDCS on hot cognition might be more indirect, and relate to higher-level cold cognitive processes such as cognitive control. A second study reported that DLPFC tDCS acutely decreased threat vigilance, similar to the effects

of anxiolytic drugs (Ironside et al., 2015). Importantly, this study found no effect of tDCS on any emotion processing task usually affected by antidepressant medication. These results suggest that tDCS may affect top-down cold cognitive mechanisms, such as attentional control, with possible indirect effects on hot cognition, but not bottom-up hot cognitive processing, which is consistent with the results of Chapter 3.

Therefore, while our measure of hot cognition was not affected by acute tDCS administration, the conclusions of Chapter 3 should be treated with some caution: tDCS does not appear to alter low-level hot cognitive processing, but it remains possible that it may affect cognitive control over low-level emotional responses.

7.4.2 Effect of tDCS and CBT on neural measures of hot cognition

If tDCS has more indirect effects on hot cognitive processing (via cold top-down control), this may explain the inconsistency between the results of Chapter 3 (where we find no acute effect of tDCS on hot cognition) and Chapter 5, in which we report stimulation-dependent effects of the intervention on amygdala activation and DLPFC activation during emotion processing.

In Chapter 5, there was a time-by-condition interaction, such that patients receiving sham stimulation showed decreased amygdala activation during emotion processing over the course of the study (collapsed across emotion conditions due to non-significant interactions with emotion). This was abated or mildly increased in patients receiving active stimulation. The interaction in the DLPFC (again during emotional processing) followed a similar (and clearer) pattern, decreasing from pre- to post-intervention in the sham group, but increasing in the active stimulation group. This could certainly fit with the previous reports that tDCS improves cognitive control over

emotional stimuli (Vanderhasselt et al., 2013), although we did not find any emotion-dependent effects. However, the amygdala results are more surprising: the amygdala is typically found to be hyperactive in depression (Hamilton et al., 2012) (though not in our sample: see Chapter 4). According to a meta-analysis, amygdala activation decreases following a course of antidepressant drugs (Delaveau et al., 2011), the same direction as patients receiving sham stimulation (plus CBT) in our trial. Therefore, it is possible that tDCS operates via somewhat distinct neural mechanisms in terms of hot cognition to either CBT or antidepressant drugs (and similar mechanisms to CBT in terms of cold cognitive processes, as both increased DLPFC activation). However, the lack of difference between the groups in amygdala activation at baseline complicates the interpretation of this result.

Although the neural mechanisms seem to differ between CBT and tDCS in terms of hot cognition, mood improvement from both interventions was predictable by baseline neural activation during hot cognition. Specifically, baseline amygdala activation to happy (but not fearful) faces predicted subsequent treatment response across both treatment arms (Chapter 6). This finding partially replicates previous work (Siegle et al., 2006, 2007a), suggesting baseline amygdala activation may function as a general predictor of treatment response. However, since all patients received CBT, it remains to be tested if this would extend to trials using tDCS alone.

In summary, the effects of tDCS on hot cognition in this thesis are not straightforward: on the one hand, the strong evidence for a lack of an effect of tDCS on low-level hot cognition is supported by previous work; on the other hand, the results of our trial indicate that CBT, but not tDCS, decreases amygdala and DLPFC

activation during emotion processing. Additionally, greater amygdala activation to positive stimuli predicted mood improvement in both groups.

In future, it will be important to delineate task-specific differences in hot cognitive processing during tDCS. In this thesis, the task in Chapter 3 differed in several important ways from the task used in Chapters 4 through 6: the most important of these was that it measured explicit (rather than incidental) emotion processing. The incidental scanner task (in which participants were required to focus on the gender, not the emotion, of the face) may have required a greater degree of top-down control to supress emotion-related activation in order to perform the task efficiently. Additionally, since only threat vigilance was acutely affected by tDCS in a previous study of several emotion-processing tasks (Ironside et al., 2015), it would be useful to include this as a measure in future clinical trials, characterising the effects of tDCS on threat-related neural activation, and potentially testing whether immediate effects of tDCS on threat-related activation could predict subsequent mood improvement from tDCS.

7.5 Implications for clinical treatment and development of interventions

Having discussed the implications of this thesis for the cognitive and neural mechanisms of depression, I will now address its relevance for clinical treatment development. First, I will discuss whether this work supports the use of tDCS as an augmentative therapy to CBT in depression. Then, I will outline the significance of our findings for treatment response prediction in depression, and make suggestions for development of novel treatments in psychiatry in general.

7.5.1 Should CBT be augmented with tDCS in depression?

This thesis does not provide strong evidence that tDCS should be used to augment CBT for depression. Unfortunately – for the purposes of clarity – it also does not provide strong evidence against this prospect. In our trial, patients who received active tDCS showed a non-significant improvement in mood (HAM-D) over those receiving sham. This lack of effect does not support hypotheses emerging from the preceding chapters' findings: from Chapter 3, the suggestion that tDCS might improve cold cognition (which according to the model should have knock-on effects on mood, as found in cognitive training studies (Davis et al., 2001; Loewenstein et al., 2004; Sitzer et al., 2006)); and from Chapter 4, the hypothesis that increasing DLPFC activity with tDCS would increase resilience against depression.

It is likely the trial was underpowered to detect a clinically relevant effect, as discussed in Chapter 5, but it is also possible that the addition of more patients would have revealed a clearer null effect. Therefore, it would be premature to draw any strong conclusions, despite the odds ratios for response and remission (2.16 and 3.65, respectively; though note the confidence intervals were very wide: 95%CI=0.59—7.99, and 95%CI=0.63—20.96, respectively). It might be useful to conduct a similar trial using a higher dose of tDCS (for example, 2mA for 20 CBT sessions), since previous work suggests higher tDCS doses tend to produce larger effect sizes (Brunoni et al., 2016). Alternatively, it may be the case that tDCS is not the optimal technique to enhance cold cognition in CBT for depression.

If tDCS is not the ideal augmentative technique, enhancing CBT by improving cold cognition could still prove useful. Both modafinil and erythropoietin could be ideal augmentative therapies for CBT, as both improve measures of cold cognition in

depression and are associated with few side-effects (DeBattista et al., 2004; Miskowiak et al., 2012, 2014). The cognitive neuropsychological model would predict that cognitive enhancement would improve patients' ability to engage with therapy, potentially by enhancing cognitive control. Neither has been tested in an RCT with CBT, despite evidence that modafinil improves depressive symptoms in depressed patients treated with standard antidepressant medications (Goss et al., 2013).

A second possible avenue for augmenting CBT is another type of brain stimulation: rTMS. Practically, tDCS has several advantages over rTMS, most obviously that tDCS does not have to be delivered simultaneously, and that tDCS is portable enough to transport by hand across several clinics. However, rTMS is a more established therapy for depression, with known parameters for delivery, and is established as efficacious in many patients (Carpenter et al., 2012; Loo and Mitchell, 2005). Currently, case reports suggest that it is feasible to perform modified CBT while a patient is receiving left DLPFC rTMS (Vedeniapin et al., 2010). Therefore, rTMS may prove to be more effective than tDCS for improving CBT for depression.

In sum, our results are relatively inconclusive on the matter of our primary clinical endpoint, whether tDCS augments CBT for depression. However, our trial was small, and demonstrated feasibility, as well as uncovering potentially important mechanistic differences between the trial arms, most importantly about individual differences in response variability.

7.5.2 Predicting response to CBT and tDCS

It has been suggested that RCTs, in addition to being the gold standard for evaluating treatment efficacy, can also play an essential role in uncovering potential

moderators of treatment response (Kraemer et al., 2002). Here, moderators refer to a measure taken at baseline (before randomisation) that provides explanatory power over individual differences in treatment response. By definition, in an RCT this baseline measure is uncorrelated with treatment arm (Kraemer et al., 2002).

Our findings suggest several potential moderators of treatment response (Chapter 6). Most notably, working memory-associated activation in our primary *a priori* ROI – the left DLPFC, our stimulation site – showed a specific ability to predict response to our combined intervention (active tDCS + CBT), but not the control arm (sham tDCS + CBT). Therefore, the left DLPFC could be an important moderator of treatment response. If replicated in larger samples, this could eventually help allocate treatment to those patients who might be most responsive (high-DLPFC patients), and suggest that other treatment avenues should be pursued in those who might not respond (low-DLPFC patients). In addition, it would be important to test whether this measurement also predicts response to tDCS alone (in the absence of combinatory CBT).

There is also an alternative interpretation of this result: that baseline activation could index the *dose* of current required to produce a clinical response (not just whether a patient would respond or not). A third possible RCT could test this more speculative suggestion. In this trial, patients would be randomly assigned to one of two groups: a “tailored” condition; or an “average” condition, where all patients would receive the same amount of stimulation (as in all tDCS trials to date). In the “tailored” condition, patients with relatively high baseline DLPFC activation during working memory (here interpreted as those with the most susceptible cortex to stimulation) would be allocated 1 mA stimulation, as in our study. Those with lower baseline DLPFC

activation would be allocated a greater amount of stimulation (e.g., 2 mA). Dose could also be adjusted with number of sessions, or duration of stimulation. This dose-tailoring would be an interesting hypothesis to test, and could eventually inform development of a personalized brain stimulation intervention. One might also hypothesize that tailoring tDCS dose could reduce the instance of mania following tDCS for depression (not reported in any patient we tested, but found in a very small number of cases in previous trials of tDCS in depression (Brunoni et al., 2017; Loo et al., 2012)).

7.5.3 Implications for treatment development

In developing novel interventions in psychiatry, two important considerations have emerged from the past several decades of research. First, the consideration of mechanism. The serendipitous discovery of many psychiatric drugs meant that any mechanistic understanding of treatment long followed the treatment itself. This is particularly true of cognitive and systems-level mechanisms, which only emerged in in the past fifteen years. The same need not be true in novel treatment development. Instead, treatments could be tailored to specifically target a specific neural or cognitive mechanism of depression; clinical trials could be designed to measure the effect of an intervention on this specific mechanism (in addition to – or in more experimental trials, instead of – more traditional subjective clinical measures). In the case of our trial, this mechanistic tailoring (focused on the DLPFC and cognitive control) was not entirely successful, at least at the group level. Nevertheless, this general principle could be particularly useful in developing brain stimulation therapies (and, indeed, has informed development of DBS therapy for depression (Mayberg et al., 2005)).

The second consideration, variability of response, has received substantial attention in studies of existing treatments. Despite this, it is exceedingly rare to see variability explored at the treatment development stage (in fact, the structure of RCTs typically rely on testing effects at the group level, without reference to individual differences). Trial designs that incorporate measures of potential sources of response variability could lead to more tailored interventions, identifying responders at the early stage of treatment development and potentially transforming our understanding of novel treatment efficacy (i.e., what works for whom?).

7.6 Limitations and future directions

While the experiments discussed clarify the role of tDCS in depression, and test its specific use in a clinical trial, there are several important limitations to our findings. We discuss general limitations of each chapter, and how they could be improved upon in future studies, before discussing the specific limitations associated with our tDCS montage that should in future be addressed with current modelling and better characterisations of different tDCS montages.

7.6.1 General limitations

7.6.1.1 Statistical power

An influential meta-analysis found that most neuroscience research is severely underpowered (Button et al., 2013) (although note we have recently re-analysed this data to show that low power is not universal across the field, and varies substantially across subfields (Nord et al., 2017c)). We conducted power analyses in all chapters to determine sample size. Unfortunately, the issue of power still affected several of our analyses: most notably, in Chapter 5, the clinical trial was a proof-of-concept,

mechanistic RCT that was not adequately powered to detect smaller effect sizes, as seen in more recent tDCS trials in depression (Brunoni et al., 2017) (our secondary outcome, change in depression scores, was powered to detect a large effect size (d~0.9), in line with earlier tDCS depression trials (Fregni et al., 2006a)). Therefore, stronger statements about an augmentative effect (or lack thereof) of tDCS on CBT must be predicated on results from a larger trial. Similarly, in Chapter 4, our primary analyses (group comparisons) were adequately powered (~80%), but our correlation analyses had relatively low power to detect more subtle relationships between symptoms and neural activations (for small effect sizes (*d*~0.3), as reported in a previous study of ours (Lawson et al., 2016), we would have required 82 subjects per group, which would not have been feasible in the context of recruitment time and cost). This may have compromised our ability to detect relationships between DLPFC, amygdala, and sgACC activation and specific symptoms. Therefore, while we would encourage replication of our results (both negative and positive), the majority necessitate larger sample sizes (with the possible exception of our null effect of tDCS on emotion identification in Chapter 3, since we had very high power (>99%) for that analysis, even using a more conservative effect size than reported in a previous study (Ironside et al., 2015)).

7.6.1.2 Clinical populations

A second consideration is our selection of the depressed population in Chapters 4-6. We included only unmedicated patients, to allow us to make inferences about the effect of depression on neural activation (or tDCS on depression) without the influence of antidepressant drugs. However, this itself is problematic for two reasons: first, depressed patients who have previously tried antidepressant drugs but no

longer take medication (~50% of our sample) may be more treatment-resistant than those currently taking medication; second, depressed patients who have never taken antidepressants (~50%) may also show distinct cognitive profiles compared to patients who have taken medication, which in turn could have affected their response to tDCS. Perhaps most importantly, in a real-world CBT scenario, many patients with severe depression are currently medicated, and tDCS may show stronger augmentative effects in these patients than in our sample, a hypothesis supported by the additive effect of tDCS and sertraline (Brunoni et al., 2013).

Additionally, there is notable heterogeneity in our sample: while we excluded patients with bipolar depression, our patients presented with psychiatric comorbidities including eating disorders (bulimia nervosa, N=2), obsessive-compulsive disorder (N=7), GAD (N=25), and psychotic depression (N=1). Although this more accurately reflects the makeup of depressed patients in clinic than 'pure' depression, it nevertheless complicates our results, possibly adding to the mechanistic variability within the clinical group (Chapters 4-6) as well as clinical outcomes (Chapters 5 and 6). This heterogeneity increases the importance of replication of these findings in independent samples of depressed patients.

7.6.1.3 Chapter 3

Chapter 3 had several specific limitations: most significantly, we tested low-level hot cognitive in only one task (an emotion recognition task). Future studies should test a more comprehensive battery of emotion processing tasks (as well as cold cognitive paradigms), as in previous work (Ironside et al., 2015). Additionally, this was our only chapter without a patient group: the acute effect of tDCS might differ crucially in

currently-depressed patients, and may not necessarily affect healthy controls in the same manner.

There are additional controls that we optimally would have tested for in this chapter, as suggested by a previous commentary (Walsh, 2013). These include a control brain region (for example, placing the anode on the primary visual cortex), a control task, and multiple stimulation sessions. These would aid in understanding the specificity of cognitive effects of tDCS, and should be incorporated into future studies to better characterise the effects of tDCS on hot and cold cognition.

7.6.1.4 Chapter 4

An important limitation of Chapter 4 was our use of an incidental emotion processing task to measure the neural correlates of hot cognition. This may have contributed to our failure to find an effect of group on the emotion processing task. Using a different task— for example, an emotion identification task— may have yielded different results; differences in neural activation during emotion processing is a well-replicated feature of depression (e.g. (Groenewold et al., 2013), and there is some evidence that these differences extend to at-risk populations (Monk et al., 2008). It is also possible that our failure to find group differences was an effect of low power, or that it was influenced by factors related to low within-subject reliability of amygdala and sgACC activation to emotion processing (Nord et al., 2017a).

7.6.1.5 Chapter 5

Chapter 5 suffered from a number of limitations. Our aim to test the feasibility of tDCS as an augmentative treatment to CBT on the NHS led to issues inherent with trials that add on to existing treatment schedules. Patients' and therapists' schedules

frequently required that weekly sessions were missed, resulting in total durations longer than the 8 weeks initially planned. It is possible that sessions closer together would have resulted in more effective tDCS dosing. Future trials should test the effect of session timing: in fact, an optimal design might deliver multiple sessions per week, as adhered to in trials testing tDCS alone or in combination with SSRIs (Brunoni et al., 2013, 2017; Fregni et al., 2006a; Loo et al., 2012).

We also observed asymmetric attrition between real and sham groups (5 patients receiving sham stimulation dropped out of the trial, whereas only 1 patient receiving active stimulation dropped out). This is difficult to anticipate (and a good argument for conducting intention-to-treat analyses, as we did). However, our fMRI analyses could only by design include patients who completed the trial; therefore, there is a possible confounding effect of this differential dropout on some of the fMRI results, in particular those seen on the faces>fixation task in Chapter 5. Although the difference in attrition was non-significant, our study was underpowered to detect this, and future trials should take this possible pattern into consideration.

7.6.1.6 Chapter 6

The most important limitation of Chapter 6 is that the ability of baseline DLPFC activation to predict specific response to tDCS has never been reported before; therefore, it is by nature preliminary and must be replicated. In such a replication, it would also be important to establish whether this putative ‘biomarker’ predicted response to tDCS alone (and/or in combination with medication), as our trial only tested tDCS in combination with CBT.

There were also a number of limitations of our tDCS montage specifically, which affected the results of Chapters 3, 5, and 6. We discuss these below, as well as their implications for future research.

7.6.2 Limitations of our tDCS montage

When designing our RCT, at the time, the existing experimental methods for DLPFC tDCS were relatively limited. Studies typically employed two large (35 cm^2) electrodes, placing the anodal electrode over the DLPFC and the cathodal elsewhere (subraorbital ridge; the right DLPFC; or extra-encephalically). With this montage, the distribution of tDCS current is relatively diffuse, and therefore electrode placement is somewhat rudimentary (typically, as in our studies, using the 10-20 EEG system, in comparison to MRI-guided TMS coil placement). Since starting the RCT, the field of experimental tDCS has progressed substantially: today, software exists to simulate current distributions to determine optimal electrode locations, and has been employed in some experimental work (Hämmerer et al., 2016). No trial in depression has yet employed this technique, though the most recent trial used a previously-simulated current distribution study to select the optimal electrode placement technique (Brunoni et al., 2017) (however, only bifrontal montages were compared in the previous simulations, and current distributions were also shown to be highly affected by head size (Seibt et al., 2015): see Figure 7.3). Additionally, a much larger number of montages are now available, including high-density montages that claim to target particular regions with much greater specificity (Nikolin et al., 2015).

Figure removed for copyright reasons. See original publication (Seibt et al. (2015)).

Figure 7.3. Example of current distribution modelling. This figure compares four localization methods (clockwise from upper left: “F3-F4”; “Beam-F3 system”; “OLE-System”; “5-5cm-Rule” on an MNI standard head; similar figures were produced for small, medium, and large-sized heads. For each methods, the authors display the resulting electric field distribution on the cortical surface following 2 mA, injected from the anode (red) to the cathode (blue) electrode. Figure reproduced from Seibt et al. (2015).

7.6.3 Refining future tDCS montages

In future trials, use of current simulations could prove highly useful in targeting the left DLPFC: individual patient parameters could optimize electrode montage, including electrode placement (for both anode and cathode) and size. Current

simulations could also inform studies that compare the differing effects of montages. At the moment, it is unclear whether results from one RCT extend to RCTs employing a different montage. As yet, no study has compared the effect of different DLPFC tDCS montages on depression, which could contribute to substantial between-trial variability. Testing this in combination with current simulations could lend mechanistic insight into the advantages and disadvantages of different DLPFC tDCS montages for depression: for example, does the cathodal targeting of the right DLPFC in bifrontal montages hinder or help symptom improvement in depression? Arguably, the true potential efficacy of tDCS in any RCT (including ours) cannot be uncovered until the optimal delivery parameters have been established. Rigorous trials that employ techniques from advanced tDCS experimental work, such as current simulations, will be crucial to reveal the relationship between specific tDCS parameters and clinical efficacy.

7.7 Summary and general conclusion

In this thesis, I have explored the role of the DLPFC in depression, and whether DLPFC tDCS targets DLPFC dysfunction as a putative intervention for depression. Several of the studies were the first or one of the first of their kind (Chapter 3, Chapters 5 and 6): therefore these findings should be interpreted with caution before replication. Nevertheless, we observed strong evidence that tDCS did not evoke low-level changes in hot cognition, which seems compatible with the small number of previous studies on this topic (Ironside et al., 2015; Vanderhasselt et al., 2013), and may indicate a distinct mechanism from that of antidepressant medication. Our results in Chapter 4 found profound hypoactivation in the DLPFC in depression during working memory, compared to controls. These results support only a subset

of the literature on DLPFC abnormalities in depression. Many studies instead report DLPFC hyperactivation (Wang et al., 2015); as discussed, a shifted inverted U-shaped curve may account for both of these findings. We also find preserved DLPFC activation in first-degree relatives during working memory, potentially reflecting a neural mechanism of resilience, which could be directly targeted in depressed patients. We tested this in an RCT in Chapter 5, where we did not find that tDCS significantly enhances CBT in depression, and therefore cannot conclude that it should be used as an adjunct therapy in this context. However, we did establish the feasibility of applying this technique, as well as its safety and acceptability to patients. The results of Chapter 5 were qualified by the analyses in Chapter 6, which found baseline DLPFC activation predicted clinical outcome specifically to the tDCS intervention: if replicated, this could represent the first fMRI 'biomarker' for tDCS.

7.7.1 Conclusion

At the turn of the millennium, it was suggested that one of the central questions psychiatry must begin to address is: how do our treatments, including psychotherapy, work? (Hyman, 2000). This question motivated much of the work presented here. This thesis attempted to develop a mechanistic framework for testing and using tDCS in the context of depression. Unfortunately, testing the utility of tDCS in clinic is severely handicapped by variability across the field in methods and montage – an enormous challenge not solved by this thesis. In spite of this limitation, this thesis provides justification for the testing of more targeted tDCS interventions in future trials, with the tentative suggestion that patients suitable for tDCS might eventually be identified according to baseline DLPFC activation, a

prospect that (if true) would be extremely useful in the development and refinement of tDCS for depression.

The pathophysiology of most mental illness is still, regrettably, unknown. This hinders development of potential interventions, and obscures our understanding of treatment mechanisms. It also makes it all the more essential that treatment development be coupled with mechanistic insight into the possible mediators and moderators of treatment response. This thesis suggests that the techniques of cognitive neuroscience are particularly well-placed to shed light on the mechanisms of established and novel treatments in psychiatry. Perhaps the strongest recommendation emerging from this work is the utility of neuroimaging and cognitive paradigms in the context of an RCT, including for psychotherapeutic interventions. Too often, treatment development is segregated in psychiatry according to explanatory model: psychological models of mental illness inform psychotherapy RCTs; biological models inform RCTs of novel medications. This approach stymies treatment innovation. Psychological, brain circuit and cellular models of mental illness can all inform putative treatments, but frameworks that integrate insights from multiple levels could help develop radical new approaches to intervention, potentially transforming our ability to treat mental illness.

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