Self Referential Processing Following Psychological Intervention for Depression: an fMRI study

Deborah Watson

June 2014

Supervised by:

Prof P. Kinderman

Dr M. Sarsam

Submitted in partial fulfilment of the degree of Doctorate in Clinical Psychology at the Division of Clinical Psychology, Liverpool University

Acknowledgements

First and foremost I am indebted to the participants of the study. Their willingness to discuss their lives with me and their patience whilst completing a particularly repetitive scanner task made this research possible.

I owe much gratitude to Peter and May. Your insightful guidance and support kept me on track (and continued for significantly longer than you'd originally bargained for). I also extend sincere thanks to Dr. Joanne Powell and Professor Rhiannon Corcoran, whose specialist expertise and breadth of knowledge has been invaluable.

Many thanks to the helpful and welcoming staff at MARIARC, in particular, to Val. You helped me massively with the scans and were a fantastic source of knowledge and wit.

Finally, thanks to Ben, for patience, understanding and an ability to explain elementary nuclear physics to a panicking novice.

Abstract

Background: There are multiple conflicting theories of depression and clients are frequently given contradictory explanations of their difficulties. Evidence that brings together biological, psychological and social factors of depression would be particularly useful in addressing this. The current study investigates the neural correlates of self-referential processing following psychological intervention for depression. This provides neurological evidence of how a central feature of psychological models may change following therapy.

Methodology: Fourteen participants, who had received psychological intervention for depression, underwent functional magnetic resonance imaging scans whilst completing three types of cognitive task: a self-referential processing task, an other-referential processing task, and a graphical task. Participants' neural activation during self-referential processing was compared to that of ten depressed participants and twelve control participants, which had been collected for a previous study.

Results: When positive and negative self-referential processing were considered together, there was no normalisation of neural activation in the post-therapy group, despite normalisation on the BDI II. When positive and negative self-referential processing were considered separately there were fewer areas of significant neural activation during negative self-referential processing in the post-therapy group than in the depressed group. Indicating that neural activation in the post-therapy group normalised. In contrast, during positive self-referential processing, a lack of difference between the control group and the depressed group precluded the possibility of normalisation.

Conclusions: The findings provide further support for the importance of the self in models of depression. In presenting neurological evidence in relation to psychological models and psychological therapy, they help bring together biological and psycho-social models of depression. It is possible that the ongoing patterns of atypical activation during self-referential processing represent a vulnerability to future episodes of depression. Possible explanations for the valence-specific findings are discussed and these are highlighted as interesting future research questions. Limitations of the research methodology are discussed and possible directions for future research are outlined.

Keywords: self-referential processing, fMRI, depression, therapy

Contents

Word count: 25,100

1. Introduction

1.1. Epidemiology of Depression

The personal, social and economic impact of depression is considerable. Depression is the most common mental health diagnosis in community care settings (NCCMH, 2010). In a pan-European survey 7.7% of respondents reported experiencing depressive symptoms severe enough to interfere with their employment or social functioning during the past six months (Lepine, Gastpar, Mendlewicz & Tylee, 1997). Depression is associated not only with significant emotional pain, but also with life-limiting functional difficulties comparable to those associated with serious medical disorders (Wells, Sturm, Sherbourne & Meredith, 1996). The health and social care cost of depression in England in 2007 was estimated at £1.7 billion rising to £7.5 billion when lost working days were considered (McCrone Dhanasiri, Patel, Knapp & Lawton-Smith, 2008).

Co-morbidity with anxiety is common in depression; 51% of people with major depression report lifetime anxiety (Kessler et al., 1996). Depression is associated with various markers of social and economic deprivation, including unemployment, lower socio-economic status, living in housing association or local authority housing, lower educational attainment, being separated or divorced, and living in an urban environment (Singleton, 2001). It is 1.5-2.5 times more prevalent in women than men (Waraich, Goldner, Sorners, & Hsu, 2004).

1.2. Definition of Terms

Within this thesis the term "depression" is used to refer to "major depressive disorder" as defined by Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev., American Psychiatric Association, 2000). The author acknowledges that there are problems with this definition of "depression." It may be culturally biased (Halbreich et al., 2007) and it is based on an arbitrary cut-off on a continuum of psychological distress.

"Self-referential" processing is a term that is used within functional imaging research to describe mental representations of the self and cognitive processes relating to the self. It is particularly relevant to the study of depression because of the central role that representations of the self (Hollon & Beck, 1979) and cognition about the self (Hollon & Beck, 1979; Mor & Winquist, 2002) play in depression.

1.3. Psychological Approach

The author does not aim to reduce the experience of depression to atypical patterns of neural activation. Nor does she wish to imply a causal role for physiological factors that correlate with cognitive features of depression. Depression is a complex phenomenon that is best understood within its psychological and social context (Kinderman, 2005). However, physiological support of psychological models may be particularly important because it provides a way of bringing together disparate research findings and models.

1.4. Intervention for Depression

In the guidelines *Depression in Adults* The National Institute of Clinical Excellence (NICE, 2009) recommend that people experiencing sub-threshold and mild to moderate symptoms are offered low intensity interventions, including guided self help, computerised cognitive behaviour therapy and group physical activity programmes. The guidelines also recommend that medication is avoided for this group as the associated costs are thought to outweigh the potential benefits. For moderate to severe depression NICE guidelines (NICE, 2009) recommend that medication is offered in conjunction with high intensity CBT or interpersonal therapy (IPT). Mindfulness based cognitive therapy is recommended for people who are not currently depressed, but have experienced 3 or more periods of depression.

There is significant research supporting the efficacy of CBT (Butler, Chapman, Forman and Beck, 2006) and IPT (Cuijpers et al., 2011). Less is known about outcomes for psychodynamic psychotherapy and counselling for depression (NICE, 2009), although both are offered by the NHS. Cognitive behaviour therapy, IPT and medication have generally been found to have comparable outcomes, although psychological therapy is associated with a reduced drop-out and reduced risk of relapse (NICE, 2009).

1.5. Competing Models of Depression

Depression has traditionally been explained by disparate and often competing models. These include models from medical/biological and psycho-social perspectives. Typically, medical models of depression are associated with viewing the symptoms of mental health difficulties as the result of pathological functioning (Patil & Giordano, 2010) and focus on biological interventions to alleviate the symptoms of depression (Patil & Giordano, 2010). In comparison, psycho-social models use psychological formulations to situate mental health difficulties within the context of individual experience. In this context mental health difficulties are viewed as understandable reactions to circumstances, and diagnoses such as depression describe one end of a continuum of human functioning (Bentall, 2004).

Clients accessing mental health services may be given multiple explanations for their difficulties from different professionals (Kecmanovic, 2011). Predictably, psychologists are more likely to favour psychological models, whilst professionals from a medical background, are more likely to favour medical explanations of psychological distress (Fulford & Colombo, 2004). These competing models could lead to confusion for clients (Kecmanovic, 2011) and may obstruct cohesive team working.

The biopsychosocial model of disorder (Engels, 1977) emphasises the roles played by a combination of biological, psychological and social factors in the aetiology and maintenance of mental health difficulties. The model is accepted by much of the academic community as a key framework for understanding mental health

difficulties (Ghaemi, 2009; Pilgrim, 2011). However, it neither specifies the putative mechanisms of biological, psychological and social factors, nor suggests ways in which these factors may interact. Elements of the model are often viewed as acting independently (Frewen, Dozois & Lanius, 2008), which has led to a fragmented body of knowledge with little communication between researchers within the separate fields (Kecmanovic, 2011). Ghaemi (2009) suggests that without a clear way of integrating the research, clinicians focus on the biological, psychological or social according to personal preference rather than through evidence based reasoning. However, it has been suggested that research on mental health continues to be dominated by biological reductionism (Read, Bentall & Fosse, 2009).

Kinderman (2005) proposes a model that specifies in more detail the role of biological, circumstantial (personally significant life events), social and psychological factors in the development of mental health difficulties. The model situates psychological processes as the intermediary between biological, circumstantial and social factors and views such processes as "the final common pathway" in the development of mental health problems. Within the model biological, circumstantial and social factors affect psychological content and processes thus leading to psychological distress. The model would therefore predict that recovery from depression is always accompanied by changes in psychological processing.

Recently newer technologies have begun to elucidate the relationships between the biological, psychological and social aspects of mental health. Advancement in

genetic technology has facilitated the investigation of the complex relationships between genetics and environment. Similarly, imaging techniques, such as functional magnetic resonance imaging (fMRI), have provided a means of exploring neural activation corresponding to psychological processes. This has enabled researchers to explore links between the psychological and the biological.

Much of the biological research on depression has been from a neurochemical perspective and focussed on the role of serotonin (5-HT) on the development and maintenance of depression. Such research has been fuelled by the antidepressant effects of medications that act on the serotonergic system. A blunted neuroendocrine response to 5-HT is consistently found in people with depression (Sharp and Cowen, 2011) and has been reported following recovery from depression (Bhagwagar, Whale and Cowen, 2002). In keeping with these findings, positron emission tomography (PET) studies report lower levels of 5-HT_{1a} receptor sites in the brains of depressed people and people who have recovered from depression (Sharp and Cowen, 2011). A common interpretation of these findings is that people with depression have a neural chemical imbalance that can be corrected by medication. However, there is evidence that psychotherapy can also impact on neurochemical functioning (Gabbard, 2000). For example, Lehto and colleagues (2008) report that following 12 months of psychoanalysis participants had increased numbers of serotonin transporters.

More recent research investigating biological aspects of depression has focussed on the role of the hypothalamus-pituitary-adrenal (HPA) axis. This is a

neuroendocrine system comprising the hypothalamus, pituitary glands and the adrenal glands, which releases hydrocortisone (cortisol) in response to stress. The principal neurotransmitters involved in regulating the HPA axis are serotonin, dopamine and norepinephrine. Childhood trauma has been associated with sensitisation of the HPA axis (Heim, Newport, Bonsall, Miller & Nemeroff, 2001) and increased activity of the HPA axis has been reported in people with depression (Heim, Newport, Mletzko, Miller & Nemeroff, 2008). It has been suggested (e.g. Heim et al., 2008) that the sensitisation of the HPA axis that is associated with childhood trauma is a risk factor for the development of depression in the context of subsequent stress.

Researchers have reported an association between major depressive disorder and neural atrophy, specifically atrophy of the hippocampus (Cole, Costafreda, McGuffin & Fu, 2011). There is evidence that this atrophy is present in first episode depression (Cole et al., 2011) and in non-depressed people who are considered at risk of developing depression due to family history and experience of childhood adversity (Chen, Hamilton & Gottlib, 2010). These findings have been linked to the increased activation of the HPA axis that can be found in depression, as cortisol is associated with hippocampal atrophy and reduced hippocampal neurogenesis (McEwen, 1999).

Depression is associated with a degree of heritability (Levinson, 2006), but attempts to find a main effect for genes have not been fruitful (Heim and Binder, 2012). The relationships between implicated genes and psycho-social factors are complex (Heim and Binder, 2012). However, recent technological improvements in

the field of genetics are furthering our understanding of epigenetic mechanisms within mental health. Research investigating gene × environment interactions, and gene × gene × environment interactions, suggests that there may be genes that can be "switched on" by life events such as abuse (Heim and Binder, 2012). For example, Caspi and collagues (2003) report that carriers of the short 5-HTTLPR allele are more likely than non-carriers to develop depression if they are exposed to stressful life events and childhood maltreatment. Although it is worth noting that many studies have been unable to replicate this finding and some meta-analyses report a negative finding (Heim and Binder, 2012). It may be that the specific type of childhood stress is important (Karg, Burmeister, Shedden, & Sen, 2011) and it seems that the effects of a 5-HTTLPR gene can be moderated by other genes (Heim and Binder, 2012).

Viewing the genes associated with depression as merely conferring a physiological vulnerability to depression is an over-simplification. Heim and Binder (2012) review the literature in this area and suggest that certain genes are associated with a greater sensitivity to environmental factors during specific periods of development. In the context of negative early experiences these genes are associated with depression, but in the context of enriching early experiences they are associated with particularly positive outcomes.

Psycho-social models of depression describe how life experiences may lead to unhelpful mental representations and problematic patterns of relating to others, which can in turn lead to the development of depression. There are numerous psycho-social

models of depression that stem from a range of psychological theories. The concept of self-referential processing fits most comfortably within cognitive behavioural theories of depression, including "third wave" mindfulness based theories, and for that reason this thesis will focus on cognitive behavioural models of depression.

Beck's (1967) cognitive model of depression postulates that there are reciprocal relationships between affect, cognition and behaviour, which can escalate difficulties in all of these areas (Beck, 1971). At the heart of the cognitive model is the concept of schemata, which are cognitive structures that process incoming information (Beck, 1976). Negative events in early childhood, or later, may lead to the development of maladaptive schemata, which underlie the development of mental health difficulties (Beck, 1976). Hollon and Beck (1979) suggested that the schemata of people with depression are typified by negative representation of the self, the world and the future. This is known as the negative cognitive triad (Hollon & Beck, 1979). Cognitive behaviour therapy aims to alter behaviour by altering cognitions (Dozois & Dobson, 2001). Client and Therapist work collaboratively on noticing unhelpful cognitions, finding evidence to test their validity, replacing maladaptive cognitions with more realistic cognitions, and identifying and altering underlying maladaptive schema and assumptions (Kendall and Bemis, 1983).

Mindfulness-based cognitive theories of depression do not focus on attitudes and assumptions themselves, but rather on the importance that attitudes and assumptions are given (Segal, Williams & Teasdale, 2002). That is, it is the way that

one relates to one's thoughts, rather than the content of one's thoughts, that is viewed as particularly important. In relation to depression problems are seen as stemming from a self-perpetuating pattern of rumination, in which thoughts are viewed as reflecting reality (Segal et al., 2002). The traditional CBT approach of actively trying to change unhelpful cognitions is seen as problematic, as it gives importance to the content of cognition and thus maintains unhelpful ways of relating to thoughts (Segal et al., 2002). The NICE guidelines on depression (NICE, 2009) recommend mindfulness-based cognitive therapy for the treatment of recurrent depression. This involves developing the ability to purposefully change one's mode of relating to thoughts from one in which the content of thoughts, and their basis in reality, is given high importance, to a less value-driven mode, where one is more aware of current moment experiences and thoughts are viewed as transitory parts of that experience.

1.6. Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is a technique that allows the functional localisation of cognitive processes. The technique thus provides a way of integrating the biological and the psychological. Magnetic resonance imaging has the benefit of involving no ionising radiation, which means that it is considered safe. Unlike PET and CT scans, it does not rely on substances being ingested or injected. Additionally, the detail of MRI scans is generally greater than that of other imaging techniques, which means that statistical power is high. This section briefly outlines how fMRI scans work then discusses research investigating neural functioning associated with self-referential processing, both in participants without a mental health

diagnosis and participants with depression. Finally, research investigating neurofunctional changes associated with pharmacological therapy and psychological therapy for depression will be discussed.

Magnetic resonance imaging (MRI) scanners consist of a very powerful magnet, within which the subject is centred. During a scan, radio signals are pulsed in complex sequences at the subject. Through analysis of the emissions that result from the radio signals in the presence of the magnetic field it is possible to construct a two dimensional image of the subject. This process is repeated over consecutive slices of the brain to produce a three dimensional image. MRI is particularly useful for scanning soft tissues, which makes it suitable for producing detailed scans of the brain and brain blood flow. By producing a series of images of dynamic processes within the brain MRI can allow researchers to investigate how local neural activity changes during different psychological processes. This is known as functional magnetic resonance imaging (fMRI).

The most frequently used outcome measure for fMRI studies is the blood oxygen level dependent (BOLD) response. This relies on the magnetism of de-oxygenated blood. Approximately two seconds after a neuron becomes active there is a localised increase in oxygenated blood followed by a decrease in de-oxygenated blood. Oxygenated blood is diamagnetic (it responds to magnetic fields) but de-oxygenated blood is paramagnetic (it does not respond to magnetic fields). Paramagnetic substances degrade the MRI signal whereas diamagnetic substances do

not. This means that in neural areas where there is a high level of oxygenated blood the MRI signal is stronger. The graphical representation of this stronger signal illustrates the areas of the brain that are more active. An fMRI scan can be repeated every few seconds to allow researchers to see changes in BOLD response as a consequence of changing cognitive processes.

Research that involves comparing brain activity between participants, and combining participants into groups, can be difficult due to individual neuro-structural differences. This problem is overcome by mapping individual neural functioning onto a standardised template of the brain. This facilitates group comparisons and integration with other research. The most commonly used templates are the Talairach atlas (Talairach & Tournoux, 1988) and the Montreal Neurological Institute (MNI) map. The Talairach atlas is based on the brain of one female whose brain was smaller than average, which means that averaged sized brains must be significantly warped in order to map on to the Talairach atlas and introduces significant potential for error. In contrast the MNI map has is based on 305 healthy brains. This makes it more representative and thus minimises the potential for error due to warping.

Functional MRI can be used to investigate neural activation at rest or during specific psychological processes. The investigation of specific psychological processes typically involves visually presented cognitive tasks presented via a mirror in the scanner. When a response is needed participants respond via button presses, preferably with all potential responses being given by the same hand, which minimises

differences in neural activation patterns associated with gross motor movements or movement on opposite sides of the body. To minimise extraneous noise associated with neurological activation that is unrelated to the experimental task, fMRI analysis usually involves subtracting neural activation during a control condition from neural activation during the experimental condition. This is known as a "contrast." For example, a researcher interested in the neural correlates of viewing happy faces might subtract BOLD response during a condition in which participants viewed neutral faces from BOLD response during a condition in which participants viewed happy faces. This would be described as the "happy-neutral contrast" or the "happy>neutral contrast".

Cognitive activation tasks in fMRI studies use either a block design or an event-related design. In a block design stimuli from each condition are presented in a block together with rest periods in between. For example, in a study that involved three conditions all the stimuli for condition one would be presented and followed by a rest period, then all the stimuli from condition two would be presented and followed by a rest period, and finally all the stimuli from condition three would be presented. The main advantages of block design tasks are the greater statistical power they offer along with their simplicity in performing for those patients where cognitive ability is a challenge. The main disadvantage however, is that habituation to the task occurs and the level of neural activation associated with each decision falls over time (Schacter & Buckner, 1998) making condition specific differences in neural activation difficult to detect (Pilgrim, Fadili, Fletcher & Tyler, 2002). Additionally, repetition of tasks with

long rest periods is likely to increase the likelihood that participants will become bored and less task-focussed. In an event-related design, stimuli for each condition are presented pseudo-randomly with a brief rest period between each stimulus, making the task less repetitive and less susceptible to the effects of habituation than a block design task (Pilgrim et al., 2002).

1.7. Functional MRI and Depression

Koenigs and Grafman (2009) review studies investigating localised neurological functioning in depression. They report that atypical neural activation within the dorsolateral prefrontal cortex[1] (dlPFC) and the ventromedial prefrontal cortex[2] (vmPFC) has been implicated in depression. Specifically, a diagnosis of depression seems linked to resting hyperactivation in the vmPFC and resting hypoactivation in the dlPFC (Koenigs and Grafman, 2009). These atypical patterns become more similar to those of non-depressed people when depression remits (Koenigs and Grafman, 2009). Koenigs and Grafman (2009) hypothesise that this pattern relates to different localised functions. Specifically, they highlight evidence that the vmPFC may be linked to either the generation of negative emotion (Zald, Mattson & Pardo, 2002) or self-awareness (Barash, Tranel & Anderson, 2000), and

[1] Dorsolateral prefrontal cortex can refer to an area roughly covered by Brodmann areas 9 and 46 (e.g. Grahn, 2010) or to a larger area incorporating the lateral parts of Brodmann areas 9-12, 45 and 46 and the superior part of Brodmann area 47 (e.g. Zelazo and Muller, 2004).

[2] Ventromedial prefrontal cortex can refer to Brodmann area 10 (e.g. Finger et al., 2008) or to a larger area incorporating Brodmann areas 10 and 11 (e.g. Bechara et al., 1998). It is within the orbitofrontal cortex (Brodmann areas 10, 11 and 47 in humans;).

the dlPFC may be linked to the regulation of emotion through reappraisal and suppression (Ochsner, Bunge, Gross & Gabrieli, 2002; Phan et al., 2005).

The association between depression and hyperactivation in the vmPFC, a brain region associated with self-awareness, is consistent with cognitive models that stress the importance of self-related cognition in depression. The association also fits with the success of mindfulness based approaches for depression, as mindfulness is negatively associated with activation in the vmPFC (Way, Cresswell, Eisenberger & Lieberman, 2010). Atypical activation in the dlPFC, a brain region associated with reappraisal, fits with evidence concerning the efficacy of CBT, in which repeated reappraisal of events often plays a key role.

The amygdala has been associated with vigilance for negative stimuli and the direction of attention towards negative stimuli (Davis and Whalen, 2001). Consistent with the finding that depression is associated with attentional bias to threatening stimuli (Mathews, Ridgeway & Williamson, 1999), hyperactivity in the amygdala has been found in people with a diagnosis of depression in response to verbal cues (Siegle, Steinhauer, Thase, Stenger & Carter, 2002), faces showing negative emotion (Fu et al., 2004) and at rest (Drevets et al., 1992). Dannlowski and colleagues (2007) present evidence of correlation between amygadala activation and cognitive bias in depression. They recorded the amygdala reactivity to subliminally presented negative faces in 35 inpatients meeting DSM-IV (APA, 1994) criteria for acute major depression. Negative cognitive bias, as evidenced by subsequent judgements about

neutral stimuli, was associated with amygdala reactivity. Additionally, negatively biased processing was associated with more severe depression and a longer course of illness (Dannlowski et al., 2007).

1.8. Neural Localisation of Self-referential Processing

Imaging researchers have used a variety of self-related tasks to localise self-referential processing in the brain. These include recognizing one's own face, detecting one's own first name, attributing an action to oneself, recalling personally relevant information, and assessing one's own personality, physical appearance, attitudes, or feelings (Legrand and Ruby, 2009).

Not surprisingly, given the disparate nature of these tasks, self-referential processing has been linked with activation over a wide neural area (Vogeley and Gallagher, 2011). This area includes cortical midline structures (CMS) such as the ventromedial prefrontal cortex (vmPFC; BA10, BA11), dorsomedial PFC (dmPFC; BA9), supragenual anterior cingulate cortex (SACC; BA24, BA32), posterior cingulate cortex (PCC; BA23), retrosplenial cortex (RSC; BA26, BA29, BA30), medial parietal cortex or precuneus (BA7, BA31), medial orbital prefrontal cortex (MOPFC; BA 11, 12) and the pre- and subgenual anterior cingulate cortex (PACC; BA 24, 25, 32) (Northoff et al., 2006; Vogeley and Gallagher, 2011). Northoff and colleagues (2006) have argued that the CMS represent a network that is specifically related to self-referential processing. However, the CMS has also been associated

with others' mindreading, inferential processing and memory recall, suggesting that it may not be self-specific (Legrand and Ruby, 2009).

Comparing neural activation patterns when making judgements about the self to patterns when making judgements about others is the most frequently used measure of self-referential processing for fMRI studies. The other may be a friend or relative (e.g. D'Argembeau et al., 2007; Heatherton et al., 2006; Ochsner et al., 2005) or a famous person (e.g. Gutchess et al., 2007; Kelley et al., 2002; Lemogne et al., 2009; 2010; Sarsam et al., 2013; Yoshimura et al., 2010; 2013). In a review article Gillihan and Farrah (2005) suggest that the results of studies contrasting self-judgements and other-judgements in this way may reflect differences in how well each subject is known. They suggest that if the "other condition" involves a close friend or relative who the participant knows well, rather than a famous figure, there will be less chance that the resultant neural activation will be affected by how well the participant knows them (Gillihan & Farah, 2005). However, for participants with limited social contact or poor familial relationships, difficulties that are more common in people with depression, judgements about a close other may introduce other confounding variables (Sarsam, 2006).

Studies that compare neural activation when making judgements about the self and neural activation when making judgements about someone else have reported self-referential processing to be associated with altered activation in the mPFC (d'Argembeau et al., 2007; Gutchess et al., 2007; Heatherton et al., 2006; Kelley et al.,

2007), the anterior cingulate cortex (d'Argembeau et al., 2007; Gutchess et al., 2007; Heatherton et al., 2006), the precuneus (d'Argembeau et al., 2007) and diffuse areas of the frontal lobe (Gutchess et al., 2007, Heatherton et al., 2006). This supports findings that lesions in the vmPFC have been linked to deficits in self-awareness (Stuss et al., 2001).

Kelley and colleagues (2002) utilised an event-related design to investigate self-referential processing by asking participants to make judgements about whether adjectives referred to themselves (self-referential condition), the current US President (other referential condition; the study was conducted in the United States), or whether the adjectives were in upper case (capital letters condition). In the self>other contrast, self-referential judgments were linked to increased activation in the PCC (BA23) and the mPFC, i.e. when the mean BOLD response to the self-referential task was subtracted from the mean BOLD response to the other-referential task there was significant activation remaining in these areas. However, when compared to baseline, these areas showed a decrease in activation during both other-referential and self-referential tasks; i.e. when the mean BOLD responses to the self- and other-referential task was subtracted from the mean BOLD response at rest there was significant activation remaining. The difference in activation in the mPFC was specific to self-referential processing, but the level of neural activation in the PCC was similar for both self-referential processing and the case condition, with other referential processing leading to the biggest decrease in activation patterns.

The default mode network (DMN) is a network of neural areas that are active during wakeful rest, that is, when attention is not focussed on a task or on external stimuli (Sheline et al., 2009). It comprises the dorsal and lateral mPFC, medial, inferior and lateral parietal cortex, medial and lateral temporal cortices and the anterior and posterior cingulate cortex. Sheline and colleagues (2009) point out that the specific tasks that have been associated with increased DMN activity, such as perspective taking, remembering past events and planning for the future, all involve an element of self-referential processing. This association between the DMN and self-referential processing could explain the findings of Kelley and colleagues (2002) who report that both self-referential and other-referential tasks are associated with a a decrease in mPFC activity compared to baseline, but other-referential tasks are associated with a significantly greater decrease. It may be that the goal directed nature of the self-referential task causes a reduction in DMN activation, but the self-referential nature of the task means that there is significant residual activity. The other-referential task is goal directed and does not involve self-referential processing and there is therefore less residual DMN activity.

Neural activation in the mPFC has been associated with taking the perspective of others (Decety & Jackson, 2004; Ruby & Decety, 2003, 2004; Frith & Frith, 2003; Gallagher & Frith, 2003) as well as with self-referential processing. D'Argembeau and colleagues (2007) investigated whether the same neural networks are responsible for each of these tasks. They carried out an fMRI study with four conditions: 1) first person self-referential (do adjectives refer to you), 2) first person other-referential (do

adjectives refer to your friend), 3) third person self-referential (would your friend say that adjectives refer to you), and 4) third person other-referential (would your friend say that adjectives refer to themselves). They report neural activation associated with self-referential processing in the dmPFC (BA 9), the vmPFC (BA 10) and the SACC (BA 32). The difference between neural activation during self-referential processing and other referential processing was higher than baseline in the dmPFC (BA 9) and lower than baseline in the vmPFC (BA 10).

1.9. Self-referential Processing in Depression

Cognitions relating to the self are key to cognitive theories of depression. Dysfunctional views about the self are one element of Hollon and Beck's (1979) negative cognitive triad and challenging these dysfunctional views is often a focus of CBT (Kuehlwein, 2002). Additionally, depression is associated with excessive self-focus (Mor & Winquist, 2002), which may also be addressed through CBT. Evidence from fMRI studies provides further support for a disruption in self-referential processing relating to depression (Greicius, Supekar, Memon & Dougherty, 2007, Koenigs & Grafman, 2009; Lemogne et al., 2009; Sheline et al., 2009; Yoshimura et al., 2010; 2013). There is limited literature comparing self-referential processing to other-referential processing in people with depression, but current evidence suggests that depression is associated with atypical levels of neural activation in the dmPFC (BA8; Lemogne et al., 2009; Yoshimura et al., 2013), the ventral anterior cingulate cortex (BA24; Yoshimura et al., 2013), and the dlPFC (BA9 & BA46; Lemogne, 2009) during self-referential processing.

Sarsam and colleagues (2013) used an event-related fMRI methodology to investigate self-referential processing in depression. They scanned depressed participants (n=14) and controls (n=14) with no history of mental health difficulties whilst they judged whether adjectives referred to themselves or the Queen of England. Sarsam and colleagues (2013) report that during self-referential processing the depressed group showed greater BOLD response in the dmPFC (BA8). No differences were observed between the depressed and control group during other-referential processing.

In a similar study utilising a block design Lemogne and colleagues (2009) asked depressed (n=15) and non-depressed (n=15) participants to judge whether an adjective described themselves or whether it was a socially desirable trait. There was a significant group x condition effect in areas of the dmPFC (roughly corresponding to BA8) and the dlPFC (roughly corresponding to BA9 & BA46). Specifically, depressed people showed greater neural activation during self-referential processing than when deciding whether the trait was desirable. However, all of the depressed participants were taking anti-depressants, which introduces a potential confound of variables. Additionally, it could be argued, that the control decision, where participants were asked to judge whether the adjective was a socially desirable trait, may not sufficiently isolate self-referential processing; the remaining neural activation may relate to judgements about people or judgements based on episodic memory.

The DMN tends to show atypical connectivity (Greicius et al., 2009) and activation (Sheline et al., 2009) in individuals with depression. Specifically, in people with depression the DMN shows increased subgenual cingulate (BA25) and thalamic functional connectivity, with functional connectivity to the subgenual cingulate being positively associated with the length of the current period of depression (Greicius et al., 2009). The DMN is typically most active during wakeful rest, becoming less active during non-self-referential tasks, but people with depression do not tend to show this decrease in DMN activity during completion of tasks (Sheline et al., 2009). Sheline and colleagues (2009) suggest that this reflects an inability to appropriately reduce self-referent cognition in depression.

1.10. Imaging Studies of Interventions for Depression

Much of the literature investigating the impact of intervention for depression on neural activation has involved either resting state activity (e.g. Kennedy et al., 2007; Goldapple et al., 2004) or activity during emotional processing (e.g. Fu et al., 2004; 2008; Keedwell at al., 2010; Ritchey et al., 2011). This research indicates that intervention for depression is associated with a normalisation of atypical patterns of neural activation. Some researchers have reported similar changes in neural activation for both medication and psychological therapy (e.g. Fu et al., 2004; 2008), other researchers report intervention specific differences (e.g. Ritchey et al., 2011). Lemogne and colleagues (2010) investigated the effects of antidepressants on neural activation during self-referential processing and Yoshimura and colleagues (2013) investigated the effects of CBT on neural activation during self-referential processing.

Both research groups report similar normalisation effects. However, methodological issues, such as subsets of participants having repeated scans (Yoshimura et al., 2013) and small sample sizes (Lemogne et al., 2010) may have affected results. Additionally, neither research group subtracted other-referential BOLD response from self-referential BOLD response, meaning that the patterns of neural activation that they report may not be self-specific.

Talking therapy of any modality may facilitate the normalisation of neural activation, although the majority of studies in this area have investigated CBT or IPT. Models of psychological intervention highlight atypical psychological processing patterns, or representations, that can be modified through therapy. It seems reasonable to suppose that there are physiological correlates of these modifications and Kandel (1998) has argued that all successful psychotherapy must involve neuro-structural changes. Similarly, therapy has been described as a "controlled form of learning that occurs in the context of a therapeutic relationship" (Frewen, Dozois & Lanius, 2010). From this perspective it is likely that the changes associated with therapy, like all learning, are accompanied by physiological changes.

Given the relatively complex nature of the learning that that takes place in therapy, it can be difficult to identify which factors may have led to physiological changes. Any changes that are associated with psychological intervention may be attributed to general factors, such as therapeutic alliance, or to therapy-specific factors, such as seeking evidence for unhelpful assumptions in CBT (Frewen, Dozois &

Lanius, 2010). Similarly, changes may reflect the application of conscious and effortful techniques that have been learned in therapy, or they may represent unconscious processes, for example a reduced bias towards negative stimuli (Etkin et al., 2005). The use of functional MRI can go some way to addressing these issues, as it allows the investigation of neural activation during specific psychological processes. However, the complex nature of therapeutic mechanisms, and the relative infancy of research in this area, means that uncertainties remain.

Kennedy and colleagues (2007) use PET in a randomised control trial comparing localised brain glucose metabolism following intervention with either CBT or venlafaxine. They report both modality specific changes and modality independent changes. Response to both CBT and venlafaxine was associated with increased glucose metabolism in the right occipital temporal cortex and decreased metabolism in the vmPFC (BA11), the orbitofrontal cortex (BA47) and dmPFC (BA8). Metabolic changes in these areas have been associated with depressed and euthymic states in people with depression (Goldapple et al., 2004). Response to venlafaxine was associated with increased metabolism in the PCC (BA29), whereas response to CBT was associated with decreased metabolism in this area. Conversely, response to CBT was associated with increased metabolism in the left inferior temporal cortex (BA20, BA21), whereas response to venlafaxine was associated with decreased metabolism in this area. Further CBT specific metabolic changes were observed in the thalamus, vmPFC (BA32), and the right occipital temporal cortex (BA19).

Goldapple and colleagues (2004) used fMRI to compare change in at-rest neural activation patterns following CBT and pharmacotherapy (paroxetine). They report that CBT is associated with increased activation in limbic areas, including the amygdala, which have been associated with encoding of emotional stimuli (Hammen, 2001) and positive and negative reinforcement (Murray, 2007), and decreased activation in neocortical areas, including the dlPFC (BA9, BA46), the ventral PFC (BA47, BA11) and the mPFC (BA9, BA10, BA11), which are associated with "higher functions" such as reasoning, speech and emotional expression (Fuster, 2008). Paroxetine was associated with changes in similar areas, but in the opposite direction. Goldapple and colleagues (2004) interpret these results in the context of theories associating CBT with "top-down" (cortical then limbic) changes, and medication with "bottom up" (limbic then cortical) changes.

Researchers investigating the impact of psychological and pharmacological intervention on emotional processing have reported similarly modality-specific findings. Fu and colleagues (2004) use an event-related design to investigate affective processing before and after pharmocological intervention (fluoxetine) for depression. They scanned people with depression (n=19) and matched controls (n=19) at baseline and again eight weeks later. In the inter-scan period people with depression received fluoxetine. Fu and colleagues (2004) report that treatment with fluoxetine is associated with a normalisation of the neural response to emotionally negative stimuli. Areas implicated include the left amygdala, ventral striatum, frontoparietal cortex and PFC. The same research group used a similar methodology to investigate the effects

of CBT for depression on the neural correlates of emotional processing (Fu et al., 2008). At baseline depressed participants (n=16) showed higher neural activation in response to negative stimuli than positive stimuli in the ACC, the right dlPFC, and the vlPFC than matched controls (n=16). Following CBT, this negative bias decreased and activation in these areas more closely resembled that of controls.

Fu and colleagues (2008) also report that higher baseline activation in the dorsal ACC in response to emotional stimuli predicted better outcome following CBT. This contrasts with the findings of Siegle and colleagues (2006) who report that CBT-related improvements were greatest in patients with relatively low pre-treatment reactivity in the subgenual ACC (BA25). These apparently contradictory findings may be due to the specific localisation (dorsal vs. subgenual) of activity within the ACC (Ritchey et al., 2011).

Keedwell and colleagues (2010) use event-related fMRI to investigate emotional processing before and after 12 weeks of pharmacotherapy (various types) for depression. They report that greater response to negative stimuli in an area of subgenual anterior cingulate cortex (sACC, BA25) was associated with a positive response to pharmacotherapy. This contrasts with the findings of Siegle and colleagues (2006) who report that a greater response to emotional processing in the sACC is predictive of a poor response to CBT. Similarly, Chen and colleagues (2007) report that increased activation in the ACC during emotional processing is predictive of a positive response to medication, whilst Fu and colleagues (2008), using the same

cognitive task, report that lower levels of neural activation in this area are predictive of a positive response to CBT. However, the discrepancy may be due to task-related methodological differences, for example whether the cognitive activation task involves explicit emotional processing or whether this emotional processing is masked by an unrelated task (Keedwell et al., 2010).

Ritchey and colleagues (2010) used a block design to investigate neural activation during emotional processing following CBT for depression. They scanned 22 depressed participants and14 control participants at baseline and 11 depressed participants and seven control participants after the depressed participants had received CBT. Ritchey and colleagues (2010) report that patterns of neural activation during emotional processing tended to normalise following CBT. Depressed participants who initially had higher activation levels within the vmPFC (BA11), and were therefore more similar to controls, were more likely to respond to CBT. However, depressed participants who showed greater negativity bias (i.e. more activation to negative than positive stimuli) in the left anterior temporal lobe (ATL; BA38) and right dlPFC (BA6), and were therefore less similar to controls, were also more likely to respond to CBT.

Ritchey and colleagues (2010) draw attention to their small sample sizes, and point out that comorbidity within their sample was high, which may have confounded results. Participants were treated to remission and this is likely to have reduced variability (Ritchey, Dolcos, Eddington, Strauman & Cabeza 2010). It is also worth

noting that the control group's second scans were not included in the analysis due to a high drop-out rate, meaning that the authors were not able to control for the effects of repeating the scan.

Lemogne and colleagues (2010) used a block design fMRI study to investigate self-referential processing in eight participants with depression and eight controls with no history of mental health difficulties. Participants were scanned at baseline (within a week of receiving antidepressant medication if depressed) and at least six weeks later. In the intervening time participants with depression received antidepressant medication of different types (SSRIs, SNRIs and tricyclics). During the scan participants were asked to judge (yes/no) whether adjectives referred to themselves (self condition) or were whether they were socially desirable traits (general condition). Lemogne and colleagues (2010) report that initially depressed participants showed greater activation in the dmPFC (BA9) and the dlPFC in the "self" condition than in the "general" condition. Following six weeks on any antidepressant medication the clinical group showed a more balanced activation in the left dlPFC, but in the dmPFC this normalisation did not occur. Continued high activation in dmPFC during self-referential processing is consistent with Goldapple and colleagues' (2004) hypothesis that modification of the activation of mPFC may be unique to CBT. Alternatively, it may be that a longer period of medication use is necessary to normalise the activity levels of the dmPFC (Lemogne et al., 2010). The areas discussed by Lemogne et al. (2010) may not be self-specific, as the "general" condition was qualitatively different from the "self" condition and did not involve other-referential processing.

The above study of self-referential processing and anti-depressant medication (Lemogne et al., 2010) is described by the authors as "a pilot study" and there are a number of limitations that should be taken into account when considering the results. The authors highlight the small sample size (eight participants per group), the heterogeneity within the clinical group, and the non-matched control group, in particular, the eight people with depression were all female and the control group consisted of five females and three males. Additionally, depressed participants were prescribed a variety of antidepressants, medication prescriptions changed over the course of the study, and some participants had their medication regime augmented by mirtazepine (Lemogne et al., 2010). Although participants were not given sedatives on the day of the scan, some sedatives may continue to have an effect on neural activation for significant periods of time. Finally, as noted by Lemogne and colleagues (2010) the scanning parameters did not allow investigation of the amygdala, which previous research has suggested is important in self-referential processing in depression. Lemogne and colleagues (2010) suggest that future research could investigate the effect of CBT for depression on neural activation during self-referential processing.

Yoshimura and colleagues (2013) used a repeated measure block design to investigate the effects of CBT for depression on self-referential processing. Participants responded via button press (yes/no) whether adjectives applied to them (self condition), were difficult to define (semantic condition), contained a target letter

(letter processing condition) or the president of Japan (other condition). Their fMRI outcome variable was the BOLD response relating to the "self" condition minus the BOLD response from the "semantic" and "letter processing condition." The "other" condition was not used in the analysis.

Yoshimura and colleagues report that at baseline depressed participants (n=23), in comparison to control participants (n=15), showed hyperactivation in the vACC and the mPFC when making self-referent decisions about negative adjectives and hypoactivation in the vACC, the superior temporal cortex and the mPFC when making self-referent decision about positive adjectives. Following CBT for depression vACC and mPFC activity during negative self-referential processing decreased and vACC, superior temporal cortex and the mPFC activity during positive self-referent processing increased. This finding is in keeping with the hypothesis that changes in mPFC activation are modality dependent and associated with CBT rather than antidepressants. Yoshimura and colleagues (2013) report that response to CBT was predicted by baseline vACC activity. Specifically lower baseline vACC activity during negative self-referent judgements was predictive of greater improvement on the Hamilton Rating Scale for Depression (Hamilton, 1980) following CBT.

Yoshimura and colleagues' (2013) findings suggest that differences in neural activation between depressed people and non-depressed people during self-referential processing are not permanent and decrease following CBT for depression. The study seems to provide convincing physiological evidence of cognitive models of

depression. However, the study involved a number of limitations that should be considered. The authors highlight the lack of reliability of the functional findings. That is the non-depressed participants, who did not undergo any intervention, showed significant changes in their patterns of neural activation at the second scan compared to the first scan. Yoshimura and colleagues (2013) suggest that these apparent experience-related changes do not necessarily affect the validity of their findings as they are in the opposite direction to the changes that are associated with CBT. However, in some contrasts the magnitude of these changes meant that depressed participants were less similar to controls at follow-up than at baseline. Research investigating the nature and cause of these changes would aid more rigorous evaluation of the findings. Nine of the participants had been involved in a previous study that utilised the same cognitive activation paradigm. This is of particular concern given the marked effects of prior scanning. Yoshimura and colleagues (2013) do not indicate whether these participants are in the depressed or non-depressed group and do not explore the potential confound that their inclusion may introduce. Additionally, the contrast that was used in the study (self-semantic-letter processing) may not have adequately isolated self-referential cognition. Finally, the authors highlight that all of their depressed participants were taking antidepressant medication and this may have affected their neural activation.

1.11. Summary and Rationale

Self-referential processing in depression is particularly important to cognitive behavioural models of the disorder and has been associated with atypical patterns of

neural activation in people with depression. Following psychological (Yoshimura et al., 2013) and pharmacological (Lemogne et al., 2010) intervention for depression, patterns of neural activation during self-referential processing tends to normalise, but research in this area is in its infancy and it is not clear to what extent methodological factors may have affected the results. It would be useful to explore self-referential processing in depression using a contrast that results in self-specific activation and avoids potentially confounding variables such as subsets of participants having prior scanning experience, mental health co-morbidity and antidepressant use. Sample sizes for fMRI studies are sometimes small. Research that asks similar questions to those already studied is of value as it opens up the possibility for larger meta-analysis.

This research moves away from the problems associated with both biological reductionism and the biopsychosocial model by elucidating links between the biological, psychological and sociological. It aims to record neural activation during self-referential processing to investigate how psychological processes may change following recovery from depression.

Research investigating the neural effects of successful psychological therapy will build evidence around the question of which elements of therapy work for specific elements of the condition, enabling clinicians to more effectively tailor interventions to individuals. Additionally, such research has the potential to lead to a more cohesive understanding of the development of depression within multi-disciplinary teams and consequently for service-users.

1.12. Aims and Hypotheses

The initial goal for this research was to build on the work of Sarsam and colleagues (2013) and Lemogne and colleagues (2010) by investigating the impact of psychological intervention for depression on neural activation during self-referential processing. Yoshima and colleagues' (2013) publication has shed some light on this. However, their findings could be complimented by research that avoids the confounding effect of re-scanning participants and utilises a contrast that effectively isolates self-referential processing such as that originally used by Kelley et al. (2002).

The hypotheses for this piece of research are as follows:

1) In a self>other contrast differences in BOLD signal change will be observed between control participants and depressed participants in the medial prefrontal cortex (mPFC), the dorsolateral prefrontal cortex (dlPFC), the posterior cingulate cortex (PCC), and the supragenual anterior cingulate cortex SACC).

2) In a self>other contrast previously depressed participants who have received psychological intervention for depression will show normalisation of BOLD signal change, that is, their patterns of neural activity during self-referential processing will become more similar to that of control participants.

3) During positive and negative self-referential processing there will be differences between control participants and depressed participants in the ventral anterior cingulate cortex, the medial prefrontal cortex and, during positive self-referential processing only, the superior temporal cortex.

4) Previously depressed participants who have received psychological intervention for depression will show normalisation of neural activity during negative self-referential processing, but not during positive self-referential processing.

5) In a contrast involving a graphical condition, such as judging whether a word is in capital letters (caps), (e.g. self negative>caps negative or self positive>caps positive) there will be between group differences in the ventral anterior cingulate cortex, the medial prefrontal cortex and, for positive words, the superior temporal cortex.

6) Previously depressed participants who have received psychological intervention for depression will show normalisation of neural activity in the self negative>caps negative contrast, but not in the self positive>caps positive contrast.

2. Methodology

2.1. Experimental Design

The research investigated neural activation during self-referential processing in people showing evidence of recovery from depression who had received some form of talking therapy. Three independent groups were involved in the study: Group 1 (control group) were those with no history of mental health difficulties; Group 2 (depressed group) were those with a diagnosis of depression; and Group 3 were those who had completed a psychological intervention for depression in the past 24 months (post-therapy group). The study was therefore a between groups design.

The study's design was somewhat different from what was originally proposed. The original intention of the researcher was to investigate the effects of CBT for depression on neural activation during self-referential processing. The original design included two groups, a control group and a depressed group. Participants would have been scanned twice, approximately 14 weeks apart, and the depressed group would receive CBT for depression between the scans. However, there were significant recruitment difficulties associated with this design (please see section 2.6 for a discussion of recruitment). In order to address these difficulties two changes were made to the design. Firstly, the exclusion criteria specifying that people should not have used psychoactive medication was removed, and secondly, people who had received talking therapy other than CBT were included. Despite these changes recruitment difficulties were ongoing and the decision was made to change the study to a three group design comprising a control group, a depressed group and a

post-therapy group. The post-therapy group included people who had previously met a diagnosis for depression, but no longer did so, and had received some form of talking therapy in the previous 24 months. The new design involved scanning participants once and carrying out between-group comparisons.

The confounding variables that were introduced by the change in design had implications for the essential research question. Specifically, the research no longer related exclusively to CBT. Participants had received various types of talking therapy, some were unsure what types of therapy they had received, and the researcher was unable to assess the extent of fidelity to the therapeutic model. Additionally, some of the participants were using antidepressant medication, or had used it in the past. The original longitudinal design would have been a methodologically robust way of addressing these issues. However, it would not have been possible within any reasonable timescale. Previous research had utilised a single time point design (Farb et al., 2010) and it was felt that such a design would facilitate recruitment and avoid the confounding effects of repeated scanning.

The outcome measure for the study was blood oxygen level dependent (BOLD) signal change relating to five contrasts: 1) self-referential>other-referential, 2) self-referential (negative)>other-referential (negative), 3) self-referential (positive)>other-referential (positive), 4) self-referential (negative)>capital letter (caps) condition (negative) and 5) self-referential (positive)>caps (negative).

2.2. Ethics

Ethical approval: The study was approved by the University of Liverpool, Division of Clinical Psychology Research Committee in November 2009. It was approved for sponsorship by the University of Liverpool in March 2010, which ensured that the research was covered by indemnity insurance. Ethical approval for research with NHS patients was obtained from North Wales Ethics Committee in May 2010 (Appendix 1).

Data storage: Records were anonymous and ciphers were stored separately as recommended by the Medical Research Council (2005). Data were stored in a locked filing cabinet or a password protected electronic file according to Mersey Care NHS Trust guidelines.

Risk: Magnetic resonance imaging does not involve ionising radiation and, providing no exclusion criteria apply, it is considered a safe procedure for both the person being scanned and for those present. (Exclusion criteria relating to scanner safety are detailed below.) Staff at MARIARC receive training on managing situations where participants become anxious in the scanner.

2.3. Major Amendments:

North Wales Ethics Committee approved two major amendments to the initial research design. The first of these involved two changes; changing the research design from a two-group repeated-measures design to a three-group design, and

including participants who had accessed therapy other than CBT and who were using antidepressant medication. This amendment was approved in February 2012. A further major amendment was approved in June 2013 (Appendix 2), which involved recruiting participants directly via the university intranet rather than recruiting through Therapists.

The amended study design is less statistically powerful, but it was believed that the amendments were required in order to address the significant differences with recruitment. Additionally, it was noted that previously published studies had used similar single-time-point methodologies (Farb et al., 2007; Farb et al., 2010) and that such methodologies avoid the problems associated with repeated scanning.

2.4. Power Analysis

The optimal sample size for an fMRI study is affected by a number of factors. These include the signal to noise ratio of the contrast under study, the number of occurrences per scan of each condition, the degree of structural heterogeneity between participants, the neural area showing activation, and the degree of functional heterogeneity between participants. Group fMRI studies typically involve 10-20 participants (Murphy & Garavan, 2004; Thirion et al., 2007) and positive findings emerging at reasonable statistical thresholds from such studies are unlikely to represent type I errors (Murphy and Garavan, 2004).

2.5. Inclusion and Exclusion Criteria

2.5.1. Inclusion criteria.

Age: Participants were required to be 18-65 years. An upper age limit of 65 years was chosen due to neurodegenerative changes in the aging brain (Good et al., 2001). This is a typical age cut-off for fMRI research. The age range of recruited participants was 18-55 years (mean=27.6, standard deviation 9.8).

English as first language: Only those with English as a first language were recruited. This is due to differences in patterns of neural activity during tasks presented in a participants' first language compared to when tasks are presented in second or subsequent languages (e.g. Kim, Relkin, Lee & Hirch, 1997). The cognitive task involved participants reading sentences presented in English, which precluded non-native English speakers from the study.

2.5.2. Exclusion criteria relating to fMRI methodology.

Medical implants: The strong magnetic fields that are involved in fMRI scans mean that participants with metallic implants such as cardiac pacemakers, stents and shunts cannot be scanned and were excluded from the study.

Pregnancy: Pregnant women were excluded from the study due to the small possibility of foetal harm relating to the MRI scan.

Frequent headaches: As a precautionary measure MARIARC protocol states that people who experience frequent headaches should not take part in fMRI research studies.

High weight: According to the local protocol at MARIARC potential participants who weighed above 20 stone were excluded from the study due to the relatively small space within the scanner.

Glasses: Due to the relatively close-fitting head coil and the high magnetic field, participants were unable to wear glasses during the scan, although wearing contact lenses caused no problems. During the telephone screening participants were told the size of the stimuli and the distance that they would be from the screen and asked whether they felt they would have a problem reading it without wearing glasses. The decision about whether to exclude them was based on their response.

Left-handedness: Neural organisation correlates with dominant hand (Carter, 1988, ch. 2, pg 78-79). Analysis of the scans involved mapping participants' scans onto a composite model of the brain. In order to ensure a reasonable level of consistency only right-handed participants were included in the study.

Neurological abnormalities: Neurological disorders may be associated with structural or functional neural abnormalities. For this reason participants with a

history of neurological problems including epilepsy, brain injury, cerebro-vascular abnormalities and meningitis were excluded from the study.

Recreational drug use: Long-term misuse of alcohol and recreational drugs is associated with neurological changes (Ishikawa et al., 1986). Participants were excluded if they met DSM-IV-TR (APA, 2000) criteria for past or present alcohol or substance misuse.

Psychotropic medication use: Participants were excluded if they had recently used medications that affect patterns of neural activation. This included the use of psychotropic medication in the four weeks prior to the first scan.

However, the guidelines of the National Institute of Clinical Excellence (NICE, 2009) recommend that for moderate to severe depression antidepressant medication alongside high intensity CBT or IPT is offered. Potential participants who had accessed primary care psychological intervention tended also to be prescribed antidepressants. In order to increase the representativeness of the study sample, and facilitate recruitment in the context of tight time constraints, potential participants for the post-therapy group were not excluded if they were taking antidepressant medication. The confound of variables that this decision introduced will be discussed in the thesis.

2.5.3. Group specific criteria.

Previous or current psychiatric diagnoses: Participants in the clinical group were required to meet DSM-IV-TR (APA, 2000) criteria for major depressive episode as assessed by the SCID-I Clinician Version (First, Spitzer, Gibbon & Williams, 2002). Participants in the post-therapy group were required to meet DSM-IV-TR (APA, 2000) criteria for a previous major depressive episode, but not for a current major depressive episode.

Psychiatric diagnoses have been associated with some degree of neuro-structural changes (Foong et al., 2001), as well as functional neurological differences (e.g. Fu et al., 2004, 2008; Sheline et al., 2009). Although there is evidence that structural and functional neurological differences decrease as psychological difficulties improve (e.g. Fu et al., 2004, 2008), this is a relatively new area of research, and represents the main hypothesis of this thesis. Therefore participants in the control group were excluded if they had ever had a mental health diagnosis.

A previous or current psychiatric diagnosis other than major depressive episode was an exclusion criterion for the clinical group and the post-therapy group. There were two exceptions to this rule. Given the high levels of comorbidity of depression and anxiety, clinical participants who met criteria for an anxiety disorder were included if the anxiety disorder was judged to be secondary to the depression. Given the strong association between trauma and depression, participants were not excluded from the depressed group or the post-therapy group if they had previously met diagnostic criteria for post traumatic stress disorder.

BDI II cut-offs: Scores of 13 and below on the BDI II (Beck Steer & Brown, 1996) are classed as "minimally depressed" and potential participants in the depressed group who had a BDI score below 14 were excluded from the study. However, potential participants in the control group and the post therapy group who had a BDI II score above ten were excluded from the study. This was done to ensure that there was sufficient difference between the groups to identify differences in neural activation.

Length of time since last therapy session

Participants in the post-therapy group were excluded if there therapy had ended two or more years ago. This cut-off point represented a balance between minimising confounding variables by scanning participants as soon as possible after therapy, and ensuring that there were enough people in the post-therapy group.

2.6. Recruitment.

2.6.1. Promoting recruitment.

Recruitment of research participants from primary care is frequently problematic (Bower et al., 2009; Salmon et al., 2007). Recruiting unemployed people, and those with a low household income, is particularly difficult (Patel, Doke & Tennakkooon, 2003). Both of these groups were over-represented in the services that were involved in the study. For these reasons difficulties with recruitment were anticipated. Prior to commencement of the study research strategies were developed to help overcome the barriers to service and client participation.

Time pressure is one of the most frequently given reasons for GP's non-participation in studies (Ross et al., 1999). However, it was necessary to place some demands on staff time as the researcher was not permitted access to clients' details without the clients' consent. In order to encourage participation in the research, the time demands were kept to an absolute minimum (5-10 minutes).

Salmon and colleagues (2007) report that GPs frequently raised a lack of relevance for their clinical work as a reason for non-participation in research. In order to address this issue communications with Therapists and Service Managers stressed the clinical implications of the research. Specifically it was emphasised that a more cohesive understanding of depression would mean that all members of a team shared the same explanatory framework and presented the same model to clients. The researcher also offered to return to the services after the study was completed to offer a training session relating to the findings of the research. Service Managers were enthusiastic about this and it was hoped that such a session would directly benefit the service for participation in the research.

Although there is a paucity of research investigating the efficacy of recruitment strategies (Bower et al., 2009), there is strong evidence that visits to research sites and face-to-face contact improves recruitment (Foy et al., 2003). The lead investigator presented at team meetings and maintained regular contact with staff to encourage participation in the study. Additionally, Therapists were emailed regularly with

updates of the study's progress and reminders about recruitment. Such feedback and reminders also seem to have a positive effect on recruitment (Foy et al., 2003).

Foy and colleagues (2003) report that identification of Research Champions can have a positive effect on recruitment. With this in mind a Research Champion was identified in both participating services who could act as the main point of contact for the researcher and promote the research within the service. In one case this was the service Research Lead and in the other case it was a Senior Therapist who had expressed a particular interest in the research.

To encourage client participation in the study participants were reimbursed for their time. The study placed a relatively large demand on the clients' time (at least two hours) and there is a degree of inconvenience and possible discomfort associated with having a scan. The researcher felt that it was important that the time reimbursement acknowledged this. However, people receiving benefits were over-represented in the services involved in the research. There is a requirement for people receiving benefits to declare all money that they receive and benefits can be stopped or reduced dependent on the amount of money that is received. After considering these issues it was felt that £20 would be a reasonable reimbursement for time, which would not affect participants' benefits. Participants were also reimbursed for travel to and from the research site.

Advice about recruitment was sought from an expert in marketing to the public sector. He emphasised the importance of personalised contact and on his advice the researcher obtained the individual email addresses of the Therapists within the service and sent regular emails directly to the Therapists letting them know how the study was progressing and thanking them for their support to date. Additionally, the Researcher took maternity leave, which enabled her to extend the recruitment period considerably. The Researcher maintained regular contact with the Therapists throughout the leave.

In a survey of randomised controlled trials investigating dyspepsia management Foy and colleagues (2003) summarised the strategies that were used to encourage recruitment. These are given in Table 2.1, together with how they were applied in the current study.

Table 2.1. Recruitment strategies (adapted from Foy et al., 2003).

Recruitment strategy	Use in current study
Adapting protocols to GPs (NHS staff) needs	Sought feedback, simplified protocol accordingly
Continuing professional education	Offered training following study
Visits to practises	Presentations at large meetings, met with Managers and Research Leads face-to-face
Financial incentives for Health Professionals	Not done
Incentives to patients	Offered financial incentive
Reminders: manualised or computerised prompts	Regular emails to remind, explored option of including reminder in discharge pack
Feedback of recruitment rates	Done through regular emails
Use of local opinion leaders	Worked with Research Champion in Service One and Lead for Research in Service two
Printed educational – newsletters and mailings	Used fliers as it was felt that these were more likely to be read than a more extensive newsletter

All of the strategies that are detailed by Foy and colleagues (2003) were put into practise in the current study, with the exception of offering payment to the Therapists for recruitment. The budget for the current study was not thought sufficient to offer payment to all Therapists who recruited. The possibility of entering recruiting Therapists into a prize draw was discussed with some Therapists, who reported that

they would resent such a strategy. They explained that they would find it patronising as it would imply that their decision to not recruit a particular participant was not based on their clinical judgement, but on a decision about what they might personally gain.

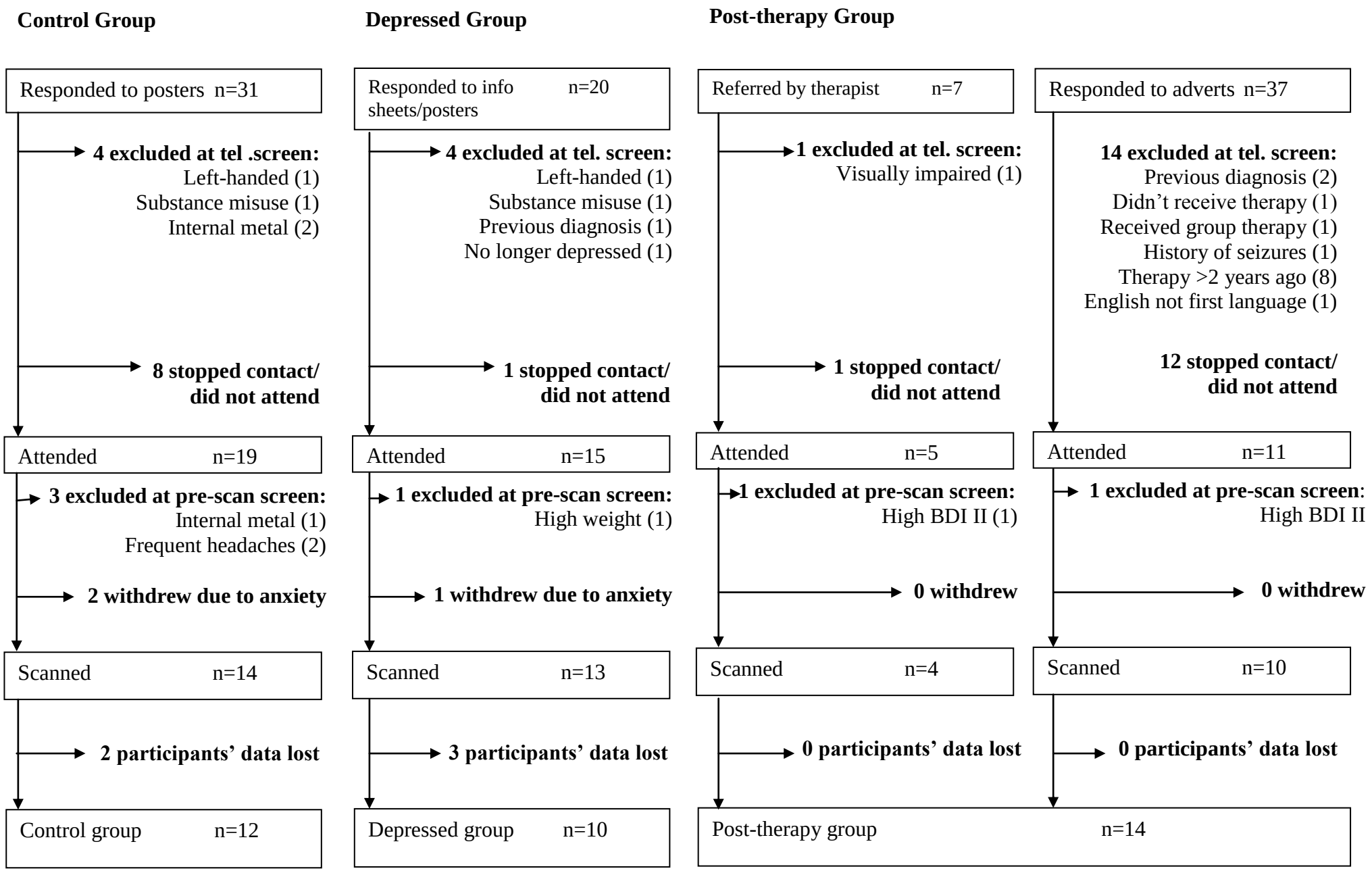
2.6.2. Group-by-group recruitment.

Both the control group and the depressed group had been previously recruited by Sarsam and colleagues (2013). However, due to missing data, the samples used for this study were slightly different from those used by Sarsam and colleagues (2013). Please see Figure 2.1 for a more detailed description of the recruitment process for each group.

Group 1: Controls

Recruitment was done through posters in the University of Liverpool and local shopping centres. Thirty-one potential participants responded and were screened by telephone. Of these four were excluded and eight stopped contact with the researcher. Unfortunately demographic information about participants who were excluded is no longer available. Of the nineteen people who attended to be scanned a further three were excluded and two withdrew from the study. The scan data from a further two participants were lost. This meant that the control group consisted of 12 participants. Please see Table 2.2 for details about the demographics of each group.

Figure 2.1: Group by group recruitment process.



Group 2: Depressed

The depressed group was recruited through Counsellors and General Practioners (GPs) within Liverpool Primary Care Trust. The professionals involved gave potential participants an information sheet about the study (Appendix 3) and sought consent for the researcher to contact them. Additionally, the study was advertised through posters in waiting rooms throughout Liverpool PCT GP practices (Appendix 4). Respondents to the posters telephoned the researcher to discuss the research further and were sent a full information sheet. Twenty potential participants contacted the researcher or agreed for their contact details to be sent to the researcher. They were screened over the telephone and had the opportunity to ask questions about the research. Of these twenty, four potential participants were excluded due the telephone screen and one stopped contact with the researcher. Fifteen people with depression attended to be scanned, but one of these had to be excluded and one withdrew from the study. As a result, thirteen people with depression were scanned. Unfortunately, the scan data for three of these participants were lost, which meant that there were ten people in the depressed group. Please see Table 2.2 for demographic details about the group.

Group 3: Post-therapy

The study was introduced to Therapists at two local Increasing Access to Psychological Therapy (IAPT) services. These are services based within pimary care that provide psychological intervention for people with relatively low levels of complexity. Clients of IAPT services tend to have a single diagnosis. Therapists at

the services were asked to give potential participants an information sheet (Appendix 5) about the study. The information sheet included contact details for the lead researcher. Interested participants contacted the lead researcher by telephone and were screened to ensure that they met the above exclusion/inclusion criteria. Eight participants who had accessed CBT for depression at steps three or four were recruited through one of the IAPT services. Of these, one participant was excluded due to visual impairment, one stopped contact with the researcher, and one was excluded as they were still depressed. No participants were recruited through the other IAPT Service (Figure 2.1).

Further participants were recruited to the post-therapy group through an advertisement on the university student intranet. Thirty-seven people responded to the advert, of which thirteen were excluded and eleven stopped contact. Eleven participants attended to be scanned, but two of these were excluded due to a high BDI II score. This meant that there was a total of fourteen participants in the post-therapy group. Three full functional scans were recorded for 12 of the participants. Two of the participants asked to stop the scan early. These participants were happy for the data that had already been collected to be used in the study. Please see Table 2.2 for demographic details about the group.

Regarding the type of psychological intervention, participants in the post-therapy group had received counselling (five), CBT (six), both counselling and therapy (two, both participants were unsure what type of therapy they had received)

and an unspecified type of therapy (one). Three of the post-therapy participants were taking antidepressant medication. Six of the participants had taken an antidepressant in the past, but were no longer taking it. (Please see Appendix 6 for more details.)

Once eligibility to be involved in the study had been confirmed an appointment was made for the participants to attend MARIARC at the University of Liverpool. Participants were reimbursed for travel expenses and received £20 for attendance.

2.7. Demographics

Table 2.2. Demographics of Participants

	Control group (n=12)	Depressed group (n=10)	Post-therapy group (n=14)
Mean age (std dev.)	26.5 (8.9)	33.8 (11.8)	29.0 (11.7)
Gender (M:F)	8:4	3:7	6:8
Mean BDI II score (std dev.)	3.8 (3.2)	29.9 (12.9)	4.3 (3.1)
Mean time since last therapy session (std dev.)	Not applicable	Not applicable	10.1 months (9.2)

Contrasts were repeated with equal-sized groups (n=10). This was done primarily ensure that any differences reported were not related to unequal group sizes, which can be a problem in fMRI research. Out of the potential participants, people were chosen according to age, then gender, and then BDI II. However, the limited

number of participants made matching difficult. Demographic information about these reduced groups is given in Table 2.3.

Table 2.3 Demographics of Equally-sized Groups

	Control group (n=10)	Depressed group (n=10)	Post-therapy group (n=10)
Mean age (std dev.)	28.0 (8.7)	33.8 (11.8)	32.3 (12.4)
Gender (M:F)	6:4	3:7	4:6
Mean BDI II score (std dev.)	3.5 (3.3)	29.9 (12.9)	4.2 (3.6)

Within the equally-sized post-therapy group (n=10) four of the participants had received counselling, three had received CBT, one had received therapy (unknown type), and two had received both counselling and therapy (unknown type). Two of this group had never used medication for mental health difficulties, five were not currently using medication, but had used an SSRI previously, two were currently using an SSRI, and for one person this information is missing.

2.8. Measures

Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Clinician Version (First et al., 2002): The SCID-I Clinician Version is a semi-structured interview designed to diagnose Axis I disorders ("clinical disorders") according to DSM-IV-TR (APA, 2000) criteria. It assesses for depressive episodes, bipolar

disorder, dysthymic disorder, alcohol or substance misuse, psychosis, obsessive compulsive disorder, post-traumatic stress disorder, eating disorders, phobias, panic disorder and generalised anxiety disorder. The time taken to complete the interview can vary from 20 minutes, for someone who reports no psychological difficulties, to several hours for people who discuss more complex psychological histories.

DSM-IV-TR (APA, 2000) was the current DSM whilst the scans were carried out. However, at the time of writing DSM V (APA, 2013) had been published. DSM-IV-TR (APA, 2000) criteria specify that a diagnosis of major depressive diorder should not be given to an individual who has suffered a significant bereavement in the previous two months. DSM V (APA, 2013) removes this "bereavement exclusion" from the criteria for major depressive disorder, but includes notes that advise clinicians to be mindful of the differences between grief and a mental health disorder.

The Beck Depression Inventory II (BDI II; Beck et al., 1996): The BDI II (Beck et al., 1996) is a widely used four-point Likert scale self-report measure that is designed to assess the severity of depression. It consists of 21 items, which are answered with regard to the previous two weeks. Scores are classified as follows: 0-13: minimal depression, 14-19: mild depression, 20-28: moderate depression, and 29-63: severe depression. The BDI II (Beck et al., 1996) takes approximately five minutes to complete. It is positively correlated with the depression subscale of Derogatis' Symptom Checklist 90-R (Derogatis, 1994), with a Pearson r of 0.89 (Steer, Ball, Ranieri & Beck, 1997). It has high internal validity (α=0.91; Beck et al.,

1996) and high one-week test-retest reliability (Pearson r = 0.93; Beck, Steer & Brown, 1996).

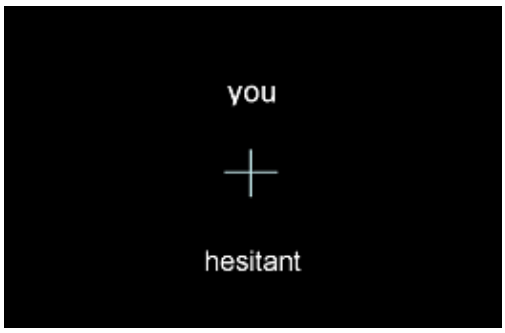
2.9. Cognitive Activation Task

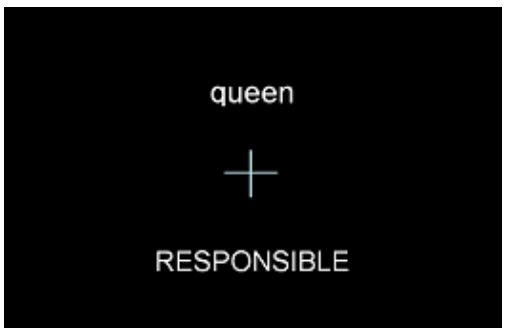
The potential for participant boredom in a block design study would be a particular problem for the current research given the association between the default mode network and self-referential processing (e.g. Raichle, 2001). Sarsam (2006) carried out a pilot study to investigate the costs and benefits of a block design and an event-related design for the current study. All participants reported becoming distracted during the block design and none reported confusion during the event-related design. For this reason an event related design was chosen as the most appropriate paradigm.

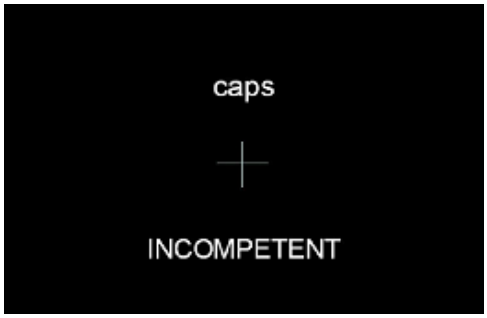
The cognitive activation task was programmed in the *Presentation*™ package (www.neurobs.com, 2001) and was displayed to the participants via a mirror mounted on the head coil of the scanner. It was developed by Sarsam (2006) based on a task designed by Kelley et al. (2002). The task was also used by Sarsam and colleagues (2013) in a study that extended Sarsam's (2006) original dataset. For continuity of data collection the same task was used in the current piece of research. Prior to the task, instructions are presented visually. The participants used response buttons to move on to the next page of instructions and indicate when they were ready to begin the task. At this stage participants had the opportunity to ask questions.

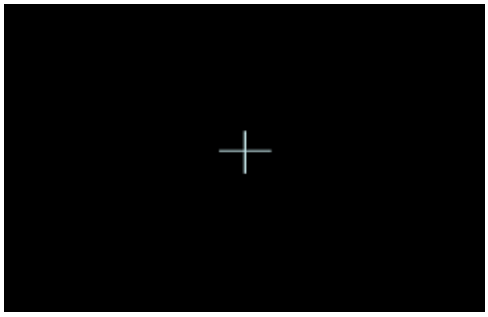
The task stimuli consisted of a fixation cross above which the task condition (SELF, QUEEN or caps) was indicated. Below the fixation cross an adjective was displayed (Figure 2.2). Sarsam (2006) chose 78 adjectives from Anderson's list of 555 personality descriptors (Anderson, 1968). The adjectives selected had a high frequency of use (over 1 in 100,000 words), and a high score for "valence" and "meaningfulness" (Anderson, 1968). The syllable length of the adjectives was balanced. They consisted of 26 positive adjectives, 26 negative adjectives and 26 neutral adjectives. The order of the conditions and adjectives was randomised. For every participant each word was used once in each condition in either the practise scan or one of the three experimental scans. This meant that there were 234 trials.

Figure 2.2: Functional MRI Stimulus Presentation. (a= self condition, neutral stimulus word; b=other condition, positive stimulus word; c=case condition, negative stimulus word; d=Rest interval; from Sarsam et al., 2013).

a 

b 

c 

d 

Participants were asked to indicate (yes/no), via the button box, whether the target adjective referred to themselves (SELF condition), the Queen of England (QUEEN condition), or was written in capital letters (caps condition). This third task was included to check task-adherence, as graphical decisions (for example, whether a word is written in capital letters) and semantic decisions (for example, whether an adjective applies to the self) have been reliably associated with specific patterns of brain activity (Kelley et al., 2002). Each task stimulus was displayed for 3 seconds. A crosshair was presented between stimuli for 3.5, 4 or 4.5 seconds (mean=4). This jittering of the stimuli allowed for optimal sampling of the BOLD response.

2.10. Research Procedure

2.10.1. Reimbursement for time and travel

On arrival at MARIARC potential participants were met by the researcher and were reimbursed for their time (£20) and given information about how to claim for travel expenses.

Completion of pre-scan interview and psychometrics.

SCID (First et al., 2002): The pre-scan interview was conducted in a clinic room at MARIARC. Prior to commencing the psychometric assesssments participants were required to give informed consent to participate in the study (see Appendix 7). The confidential nature of the research was explained to the participants, as were the limits of confidentiality. That is, the participants were told that if they revealed something that suggested that they, or someone else, was at risk of harm, the researcher would be obliged to share this information. Participants were reminded that although the data were scored anonymously, all scans were reviewed by a radiologist and if the scan revealed abnormal findings a key would be used to identify the participants and the information would be shared with their GP. Additionally, participants were reminded that they were free to leave the study at any point without specifying a reason and that this would not affect any reimbursement that they received. They were given an opportunity to ask any questions that they had and were encouraged to ask further questions as they arose.

The SCID (First et al., 2002) was conducted without adaptation and according to the manual protocol (First et al., 2002). Prior to beginning the SCID (First et al, 2002) participants were informed that it was a measure used to diagnose psychological difficulties, but that it was unlikely to reveal anything of which they were unaware. Sarsam (2006) reports that one of the control group revealed a history of trauma for which she had not accessed support. She agreed that the information be shared with her GP with a recommendation that she be referred to local trauma services. None of

the participants who were specifically recruited for this research, that is the post-therapy group, revealed previously undisclosed information.

BDI II (Beck et al., 1996): Participants were told that the BDI II is a measure that is frequently used to assess the severity of depression. They were handed the measure and the researcher clarified that it referred to the previous two weeks.

Reading ability: Due to the nature of the cognitive activation paradigm participants were required to reach a minimum level of reading ability. Reading ability was not recorded as a variable; rather participants were screened to ensure that they reached a minimum level of reading ability and could therefore engage with the cognitive activation paradigm.

The control group and the depressed group were asked to read the first column of the National Adult Reading Test (NART; Nelson & Willison, 1982). This is not a measure of reading ability per se, but a tool used with people with brain injury to assess premorbid IQ. Participants were required to make less than six errors reading the first column of the test only. All potential participants reached this requirement. In the post-therapy group participants were asked to read aloud the first question of the BDI II without making mistakes. All potential participants met this requirement.

Neither procedure equates to a specific level of reading ability, and therefore they cannot be directly compared. Both approaches were informal techniques to

ensure that participants would be able to engage with the cognitive activation paradigm. The reason for the change in the methodology was to minimise the time required from participants to complete pre-scan measures.

Exclusion from the study due to pre-scan psychometric results: Participants whose psychometric results meant that they did not meet the study's inclusion criteria still received reimbursement for their time and travel.

Scan: Prior to the scan, potential participants met with a radiographer who completed a full screen according to MARIARC protocol to check whether it was medically safe for them to be scanned. This involved checking for the following exclusion criteria: pregnancy, high weight, frequent headaches and metal implants.

Due to the loud noise emitted by an MRI scanner participants were provided with earplugs. They were given the response device in their right hand and a panic button in their left hand.

2.11. Image Acquisition

All MR images presented in this thesis were acquired using a Siemens Trio 3.0 Tesla whole body magnetic resonance scanner, with an eight channel phased array head coil (MARIARC, University of Liverpool, UK).

The study involved four functional MRI scans and a structural scan onto which the functional scans were mapped. The structural scan (4 minutes 23 seconds) was a

high resolution T1-weighted scan with slice selective inversion recovery with iPAT factor 2 and water excitation. It was based on an MP-RAGE sequence (used previously by Mugler and Brookeman, 1990) with the following parameters: 176 slices acquired sagittally, TI=1100, TE: 5.57ms, TR 2040ms, flip angle 8 , bandwidth 130HX/px, voxel size 1x1x1mm.

The anatomical scan was followed by four functional scans. The first of which gave the participants opportunity to practise the cognitive task. Functional images were obtained using a T2-weighted single-shot echo-planar imaging (EPI) sequence (TE=3ms, TR=2000ms, flip angle 80 , slice thickness 3.5mm, 0.35mm gap, matrix 64x64, FOV=224x224mm^2, in plane resolution 3.5x3.5mm, 28 axial slices). Images were collected in an interleaved sequence, first the even numbered slices were collected and then the odd numbered slices were collected, for example 2, 4, 6 ... 28, 1, 3, 5 ...27

2.12. Functional MRI Data Processing and Analysis

Pre-processing: Data for the clinical group and the control group had been collected previously (Sarsam et al., 2013) and analysed using Brain Voyager (Goebel, Esposito & Formisano, 2006; Formisano, Di Salle & Goebel, 2006). However, these data were re-analysed using the Statistical Parametric Mapping software package (SPM8; Friston et al., 2007), available at: Welcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm. SPM8 was used for all stages of pre-processing (i.e. slice-time correction, realignment, normalization and

smoothing) and for statistical analysis of the fMRI scans. This was done because SPM8 is considered superior to Brain Voyager for making group comparisons (Wall, 2011) and has been more frequently used in published research. SPM8 (Friston et al., 2007) is based on the general linear model and allows voxel-by-voxel comparison of three dimensional images. It can be used to perform a number of statistical tests based on the general linear model including T-tests, ANOVAs, correlations and regressions.

The raw DICOM data were first imported into SPM8 and converted into a format used by SPM8 (Friston et al., 2007; "Nifti format"). Slice-timing correction was applied to the functional images to account for the fact that slices are collected at a slightly different time. (It is not possible to scan the slices that make up each whole-brain image at exactly the same time, but later analysis assumes that each whole-brain image represents BOLD response at a single time point. Slice time correction corrects for this assumption by taking account of whether the slices were collected in a top down or bottom up sequence and whether they were collected sequentially or in an interleaved sequence and making consequent adjustments to the data.) Functional images across the four time series were re-aligned to the first image of the first time series to correct for head movement during and between scanning sessions. During realignment a mean functional image volume is constructed from the realigned images for each participant.

Coregistration is the next pre-processing step. This involves coregistering the structural (T_1 weighted) image to the mean functional image (the mean EPI image).

The individuals T1-weighted image is then segmented using the VBM toolbox (VBM8). The grey matter segment is then normalised to the a priori grey matter template supplied by SPM. The result parameters are then applied to the functional images to normalise the T1-weighted image and functional images into MNI space. This allows each individual's neural activation to be directly compared to that of others.

Finally, the data were smoothed using a 5mm full-width half maximum (FWHM) Gaussian kernel to help minimise the impact of extraneous noise.

Analysis: All analysis was carried out using SPM8 (Friston et al., 2007). The smoothed images for each individual were first entered into a first-level design matrix. For each participant six T contrasts of condition-specific BOLD response were performed; 1) other>caps, 2) self>other, 3) self negative>other negative, 4) self positive>other positive, 5) self negative>caps negative and 6) self positive>caps positive For example, in the "other>caps" contrast the BOLD response in the "caps" condition was subtracted from the BOLD response in the "other" condition to determine whether the two conditions were associated with different patterns of neural activation.

The probability threshold was set at $p<0.001$ uncorrected. This probability (0.001) is the default setting for uncorrected comparisons in SPM8 (Friston et al., 2007) and is used as standard in published analyses of the whole-brain (e.g.

Dannlowski et al., 2007; Gutchess et al., 2007; Yoshimura et al., 2013). It was used in the current study as to facilitate integration with existing research. In order to avoid type II errors the analysis was uncontrolled for multiple comparisons. The possibility of type I errors was controlled by setting a minimum cluster size of eight voxels, which was based on the voxel size of the original fMRI data ($47mm^3$). This minimum cluster size was used by Sarsam and colleagues (2006; 2013) and thus facilitated integration of results. It was felt that this cluster size (approximately $400mm^3$) would minimise type I errors as voxels containing false positives arising by chance are likely to be scattered throughout the SPM, rather than clustered together. A relatively small cluster size was used as it was felt that self-referential processing may involve a network of relatively small neural areas. For the valence-specific contrasts a minimum cluster size of 20 voxels was used (approximately 940 mm^3). This larger size was chosen to reduce the noise associated with having a relatively small number of each trial per participant.

This analysis generated six contrast images per participant. These images were imported into a second level design matrix for group comparisons. In order to explore the contrasts at a group level six independent sample T-tests (other>caps, self>other, self negative>other negative, self positive>other positive, self negative>caps negative and self positive>caps positive) were performed on the data from each group (control, depressed and post-therapy). The other>caps condition was used only to check task adherence and not included in further analysis.

Following this five one way ANOVAs were performed based on the original T-tests to explore BOLD response for the above contrasts between groups. For all ANOVAS all six possible contrasts were explored: 1) control group>depressed group, 2) control group>post-therapy group, 3) depressed group>control group, 4) depressed group>post-therapy group, 5) post-therapy group>control group and 6) post-therapy group>depressed group.) This analysis was done on a whole brain level. The probability threshold was set at $p<0.001$ with a minimum cluster size of eight voxels for the general self-referential processing contrast and 20 voxels for the valence-specific contrasts.

3. Results

3.1. Psychometric Results

NART/informal reading test: In order to ensure that they were able to engage with the cognitive activation paradigm participants were required to meet a minimum standard of reading ability. This was assessed by asking participants to read out either the first column of words from the NART with a minimum of 5 pronunciation errors (non-depressed group and depressed group) or the first item of the BDI II (post-therapy group). This standard was met by all potential participants.

Structured Clinical Interview for DSM-IV: As assessed by the SCID I/P none of the participants in the control group or the post-therapy group met DSM-IV criteria for a mental health diagnosis. All participants in the post-therapy group met criteria for a history of major depressive episode and three also met criteria for a previous diagnosis of PTSD. All participants in the depressed group met criteria for major depressive episode with one participant meeting a diagnosis of panic disorder, which was secondary to depression. This decision was arrived at in collaboration with the participant, who clarified that her low mood had reduced her activity levels and hence the frequency with which she left the house. Subsequently she had become more anxious about leaving the house and this had developed into panic disorder.

Beck Depression Inventory II: Table 3.1 shows the mean BDI II score with the standard deviation and range for each of the three groups.

Table 3.1. BDI II score by group

Group	Mean BDI II score (std deviation, range)
Control group (n=12)	3.8 (3.2, 0-10)
Depressed group (n=10)	29.9 (12.9, 14-50)
Post-therapy group (n=14)	4.3 (3.1, 0-10)

A Tukey HSD Test revealed that the mean BDI II score of the depressed group was significantly higher than that of both the control group and the post-therapy group. The mean BDI II scores of the control group and the post-therapy group were not significantly different.

3.2. Behavioural Response Results

Participants responded to 98.2% of the stimuli. The between group differences in the percentage of stimuli to which a response was given are shown in Table 3.2. An ANOVA revealed no statistically significant differences between the conditions ("self," "queen" and "caps") and no statistically significant interaction effects. There was a significant group effect ($p<0.04$, $F=3.24$). A Tukey's HSD test revealed that the only group difference between the percentage of stimuli to which a response was given that reached statistical significance was the difference between the depressed group (96.3%) and the control group (99.9; $p<0.05$).

Table 3.2, Percent of stimuli to which a response was given by group and condition

Group	Percentage of stimuli to which a response was given			
	Self	Queen	caps	Total
Control group (n=12)	99.9	99.8	100	99.9
Depressed group (n=10)	96.7	95.7	96.5	96.3
Post-therapy group (n=14)	97.6	98.2	99.2	99

Table 3.3 shows the mean response times by group and condition. Across the groups participants responded fastest to the "caps" condition and slowest to the "other" condition. An ANOVA revealed that differences between conditions reached statistical significance ($p<0.0001$, $F=23.25$). It is worth noting that the post therapy group showed a different pattern, specifically they responded fastest to the "caps" condition, but slowest to the "self" condition. Across conditions the depressed group responded slowest and the control group responded quickest. An ANOVA revealed that differences between the groups were statistically significant ($p<0.0001$, $F=12.59$).

Table 3.3, Mean response times by group and condition

Group	Mean response time (seconds)			
	Self	Other	Caps	Total
Control group (n=12)	1.46	1.70	1.27	1.48
Depressed group (n=10)	1.63	1.89	1.56	1.77

Post-therapy group (n=14)	1.86	1.80	1.33	1.58
Total	1.65	1.78	1.39	1.61

A Tukey's HSD test was used to establish which of the observed differences were significantly different. Across groups the differences between the "other" condition and the "self" condition was significant ($p<0.05$) and the difference between the "self" condition and the "caps" condition was significant ($p<0.01$). Across conditions the difference between the depressed group and the post-therapy group was significant ($p<0.01$) but the difference between the post-therapy group and the control group was not significant. In both the "self" condition and the "other" condition the differences between the depressed group and the control group were significant ($p<0.01$), but the differences between the post-therapy group and the other groups did not reach statistical significance. In the "caps" condition no differences between groups reached statistical significance.

3.3. Functional Magnetic Resonance Imaging Results

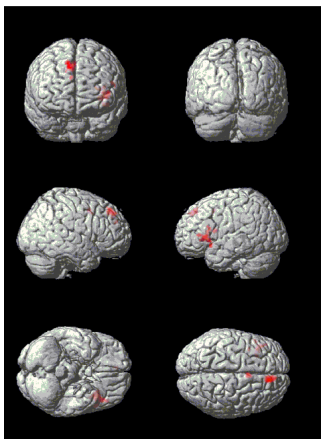
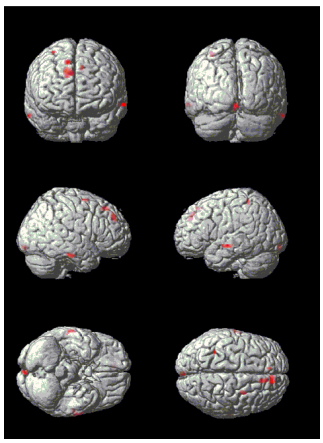
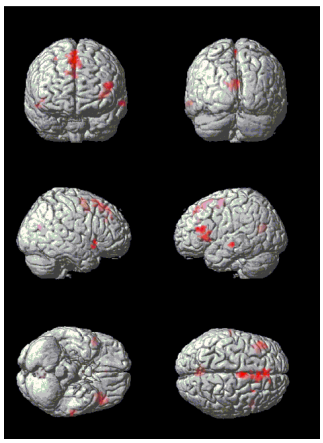
3.3.1. Task adherence.

Task adherence was monitored by performing an other>caps T contrast for each group (that is, for each voxel the mean BOLD response in the "caps" condition was subtracted from the mean BOLD response in the "other" condition). The probability was set at 0.001 uncorrected with a minimum cluster size of eight voxels. This contrast resulted in significant activation in all three groups in the superior frontal gyrus (BA8) (see Figure 3.1). The significant results across groups suggest that

participants in all groups were adhering to the specified tasks. This contrast will not be further discussed.

Figure 3.1, Other>caps contrast by group.

Results are uncorrected for multiple comparisons. Only clusters of voxels with a minimum of 8 voxels are included. P was set at <0.001. Images are imposed on a sample brain from SPM8 (Friston et al., 2007). Anterior, posterior, lateral, inferior, and superior views are shown.

		
Control group (n=12), other>caps contrast	Depressed group (n=10), other>caps contrast	Post-therapy group (n=14) other>caps contrast

3.3.2. Hypothesis one.

The first hypothesis was that in the self>other contrast differences in BOLD signal change would be observed between control participants and depressed participants in the medial prefrontal cortex (mPFC), the dorsolateral prefrontal cortex (dlPFC), the posterior cingulate cortex (PCC), and the supragenual anterior cingulate cortex SACC).

In order to investigate this two T tests, based on individual participant's self>other T-test images, were peformed: one across the control group and one across the depressed group (see Figure 3.2, first two cells). The control group showed strikingly more diffuse activation than the depressed group.

An ANOVA based on individual participant's self>other T-test images was used to investigate which of the observed differences between the control group and the depressed group reached statistical significance. For all ANOVAs only the neural areas that showed significant differences when matched groups were used will be discussed.

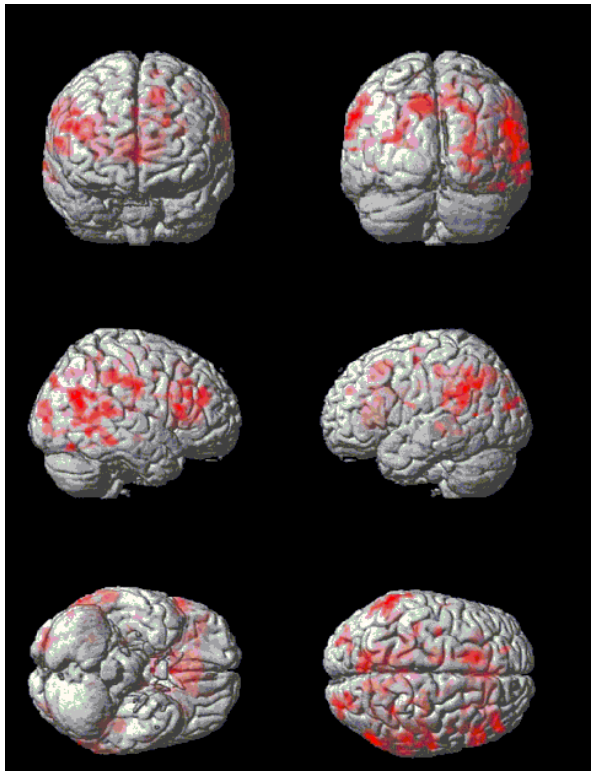
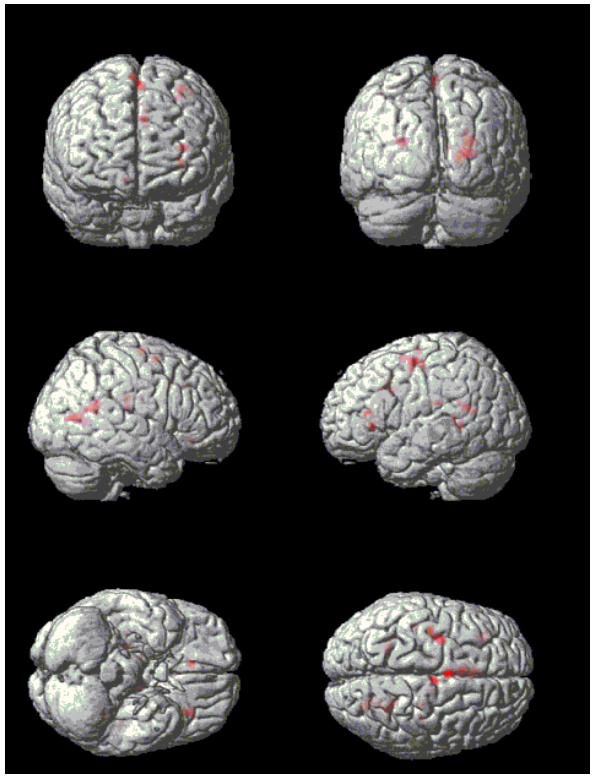
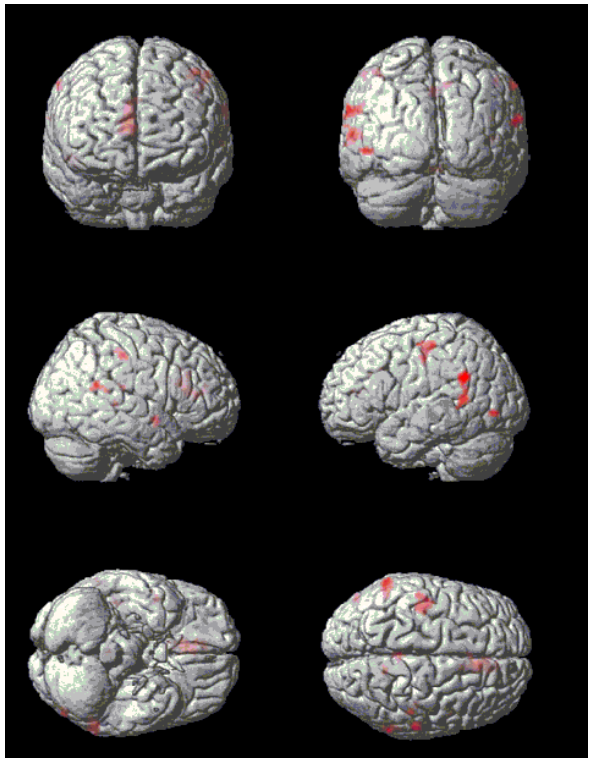
There were no areas of significantly different BOLD signal change between the control group and the depressed group in the mPFC, dlPFC or the SACC. This is in contrast to hypothesis one. In keeping with hypothesis one there was significantly greater BOLD signal change in the control group compared to the depressed group in the posterior cingulate cortex (BA31).

Further areas of greater BOLD signal change in the control group compared to the depressed grop were found across the fronto-parietal cortex (BA2, BA3, BA4, BA6, BA19, BA40, BA43; for full results see Appendix 8). There were no areas of greater BOLD signal change in the depressed group compared to the control group.

Figure 3.2 self>other contrasts across groups

Results are uncorrected for multiple comparisons. Only clusters of voxels with a minimum of 8 voxels are included. P was set at <0.001.

Images are imposed on a sample brain from SPM8 (Friston et al., 2007). Anterior, posterior, lateral, inferior, and superior views are shown.

Self>other across control group (n=12)	Self>other across depressed group (n=10)	Self>other across PT group (n=14)
		

3.3.3. Hypothesis two.

The second hypothesis was that in the self>other contrast previously depressed participants who had received psychological intervention for depression would show normalisation of BOLD signal change, that is, their patterns of neural activity during self-referential processing would become more similar to that of control participants. Given the results of hypothesis one this would mean areas of greater BOLD response in the post-therapy group compared to the depressed group in diffuse areas across the fronto-parietal cortex and the posterior cingulate cortex (BA31).

In order to investigate this a further self>other T test was carried out across the post-therapy group (Figure 3.2, third cell). The resultant pattern of BOLD signal change appeared similar to that of the depressed group; the post-therapy group does not show a more diffuse pattern of BOLD signal change than the depressed group. This suggests that normalisation had not occurred, which contradicts hypothesis two.

ANOVAs were performed to further investigate the differences in BOLD signal change between the post-therapy group and the depressed and control groups. The comparison of the post-therapy group and the depressed group revealed no areas of greater BOLD signal change in the post-therapy group than the depressed group. The depressed group had greater BOLD signal change than the post-therapy group in the posterior cingulate cortex (BA30; see Appendix 8 for full results). The minimal differences between the post-therapy group and the depressed group do not show normalisation, and are therefore not in keeping with hypothesis two.

The comparison of the control group and the post-therapy group revealed no areas of greater BOLD signal change in the post-therapy group than the control group. There were areas of greater BOLD signal change in the control group than the post-therapy group in the posterior cingulate, the frontoparietal cortex, the occipital cortex and the culmen (see Appendix 8 for full results). It is of note that the areas showing greater BOLD signal change in the control group than the post-therapy group overlap with those showing greater BOLD signal change in the control group than the depressed group. This emphasises the similarities between the post-therapy group and the depressed group, and is not consistent with the normalisation proposed in hypothesis two.

3.3.4. Hypothesis three.

Hypothesis three was that during positive and negative self-referential processing there would be differences between control participants and depressed participants in the ventral anterior cingulate cortex (vACC), the mPFC and, during positive self-referential processing only, the superior temporal cortex.

This hypothesis was investigated by carrying out two contrasts; self negative>other negative and self positive>other positive. This contrast was based on the equally sized groups (n=10). The first two cells of Figure 3.3 show the results of the contrasts for the controlled group and the depressed group. Because these data are

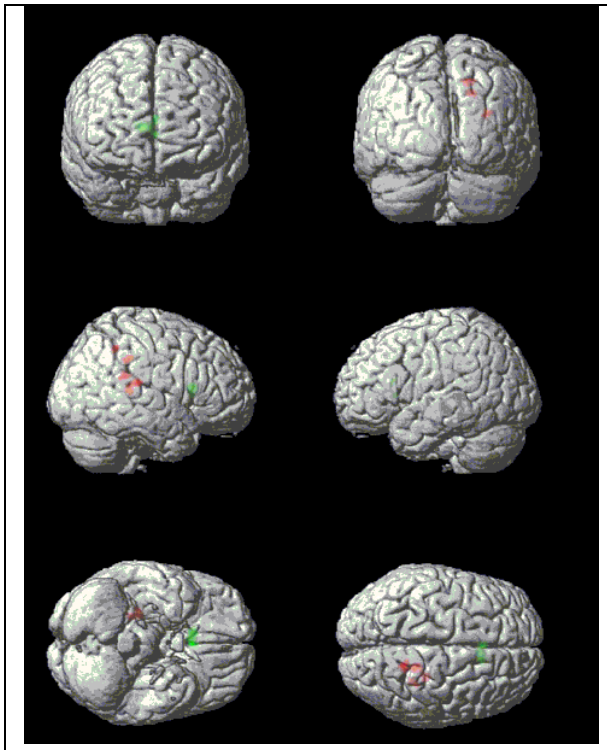
based on relatively few trials (25 per participant), the minimum cluster size was set at 20 voxels to minimise noise.

In the self negative>other negative contrast both the control group and the depressed group showed significant neural activation in the insula and the posterior cingulate cortex (Figure 3.3, first two cells). The depressed group also showed a large area of significant signal change in the inferior frontal gyrus of the frontal lobe (BA9, BA13 and BA45) in a cluster that included the dorsolateral prefrontal cortex.

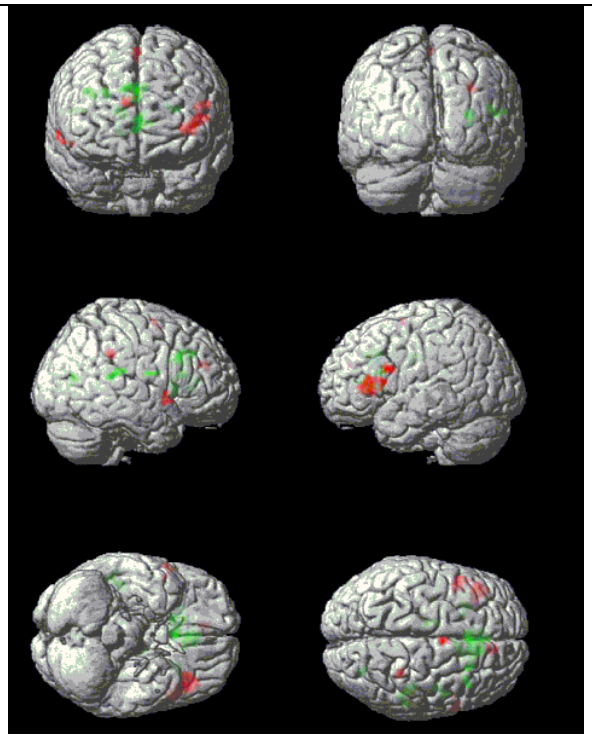
Figure 3.3, Negative (red) and positive (green) self referential processing by group

Results are uncorrected for multiple comparisons. Only clusters of voxels with a minimum of 20 voxels are included. P was set at <0.001.

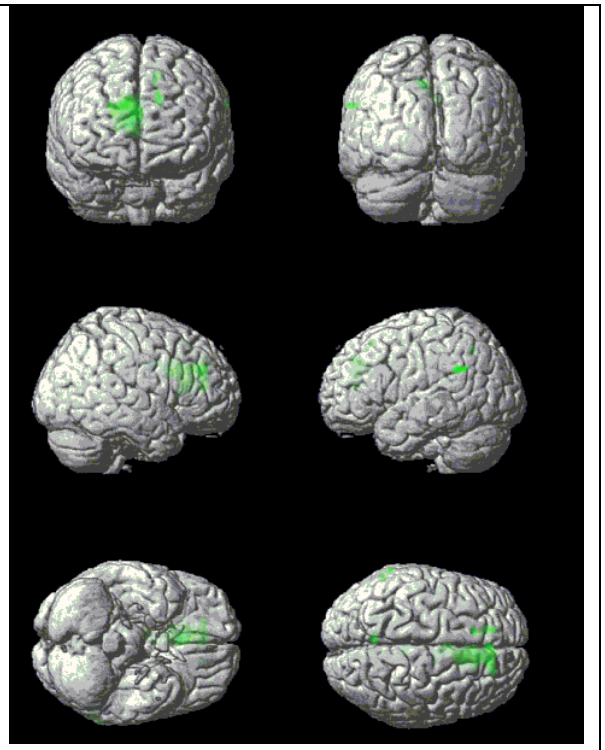
Images are imposed on a sample brain from SPM8 (Friston et al., 2007). Anterior, posterior, lateral, inferior, and superior views are shown.



Control group (n=10), negative and positive



Depressed group (n=10), negative and positive



Post-therapy group (n=10), negative and

self-referential processing	self-referential processing	positive self-referential processing

An ANOVA was performed to investigate which differences reached statistical significance. There was significantly greater BOLD signal change relating to negative self-referential processing in the depressed group compared to the control group in a large area (187 voxels) covering the inferior frontal and middle gyri of the left frontal lobe and the insula (BA13, BA46; see Appendix 9 for full details). Further areas of greater activation in the depressed group compared to the control group were found in the left inferior frontal gyrus (BA9) and the precentral gyrus (BA6). These neural areas are not in keeping with hypothesis three. There were no areas of significantly greater BOLD signal change in the control group compared to the depressed group in the self negative-other negative contrast.

In the self positive>other positive contrast both groups showed significant BOLD signal change in the anterior cingulate cortex (please see Figure 3.3, first two cells). An ANOVA was performed to explore significant differences between the groups relating to positive self-referential processing. The depressed group showed no areas of greater BOLD signal change than control group and there were no areas of significantly greater BOLD signal change in the control group compared to the depressed group. This is in contrast to hypothesis three.

3.3.5. Hypothesis four.

The fourth hypothesis was that previously depressed participants who had received psychological intervention for depression would show normalisation of neural activity during negative self-referential processing, but not during positive self-

referential processing. Given the results relating to the third hypothesis normalisation during negative self-referential processing would be a reduction in neural activation in the inferior frontal and middle gyri of the left frontal lobe and the insula (BA13, BA46), the left inferior frontal gyrus (BA9) and the precentral gyrus (BA6). No significant differences between the control group and the depressed group were found during positive self-referential processing, which precluded the possibility of normalisation.

A T test across the post-therapy group revealed relatively little BOLD signal change in relation to negative self-referential processing (Figure 3.3). This was similar to the control group and is therefore in keeping with the normalisation predicted by hypothesis four.

In the depressed group>post-therapy group contrast for negative self-referential processing there were no areas of significantly greater BOLD signal change. That is, the differences observed in the T tests between the depressed group and the post-therapy group, which are shown in Figure 3.3, did not reach statistical significance. These results do not support normalisation. There were no areas of significantly greater signal change relating to negative self-referential processing in the post-therapy group>depressed group contrast.

In the control group>post-therapy group contrast for negative self-referential processing greater BOLD signal change was observed in the precuneus (BA7; for full

details see Appendix 9), the posterior cingulate cortex (BA31), the parietal lobule (BA40), the caudate tail and the insula (BA13). These findings highlight areas of reduced BOLD signal change during negative self-referential processing in the post-therapy group. This reduced neural activation in the post-therapy group partially supports normalisation, as depression is associated with increased neural activation during negative self-referential processing. However, the magnitude of the reduction in neural activation means that the post-therapy group is significantly different from the control group. In the post-therapy group>control group contrast there were no areas of significantly greater BOLD signal change.

As noted above, the possibility of normalisation of neural activation during positive self-referential processing was precluded by the lack of significant differences between the control group and the depressed group, which is in keeping with hypothesis four. However, it is of note that there were some significant differences in BOLD signal change between the post-therapy group and the other groups. (Please see Appendix 9 for further details.)

3.3.6. Hypothesis five.

Hypothesis five was that in a contrast involving a graphical condition, such as judging whether a word was in capital letters (caps), (e.g. self negative>caps negative or self positive>caps positive) there would be differences between the control group and the depressed group in the ventral anterior cingulate cortex (vACC; BA24), the

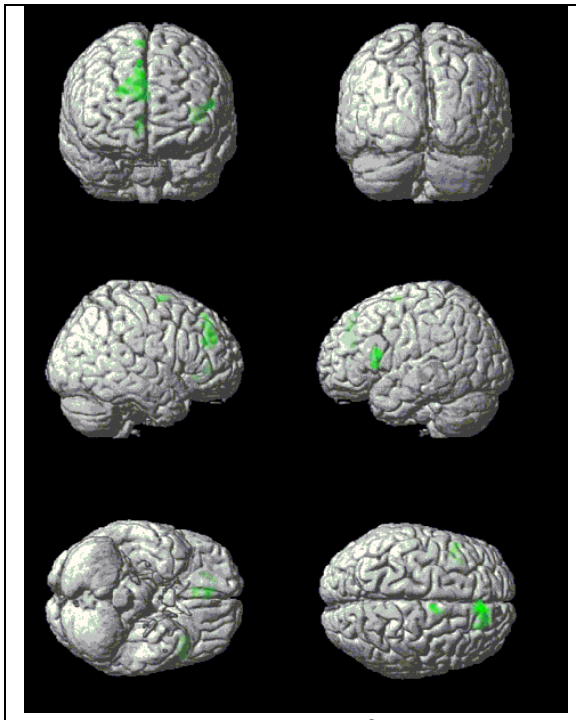
medial prefrontal cortex (mPFC) and, for positive words, the superior temporal cortex. This hypothesis was investigated using the equally-sized groups.

T tests were carried out across the control group and the depressed group to investigate the self negative>caps negative and the self positive>caps positive contrasts (see Figure 3.4, first 2 cells). In the self negative>caps negative contrast the control group showed no significant BOLD response clusters over 20 voxels. The depressed group showed a large area (733 voxels) of significant BOLD signal change in an area of the left frontal lobe including the dorsolateral prefrontal cortex (dlPFC; BA9 and BA46) and insula (BA13)and an area of the medial frontal gyrus (BA6 and BA8). In the self positive>caps positive contrast both groups showed significant BOLD signal change in the anterior cingulate cortex (BA24, BA32), areas of the right medial frontal cortex (BA6, BA9, BA11), and an area covering the inferior frontal gyrus and the insula (BA13, BA44). There were fewer significant voxels in the control group than in the depressed group (see Figure 3.4, first 2 cells).

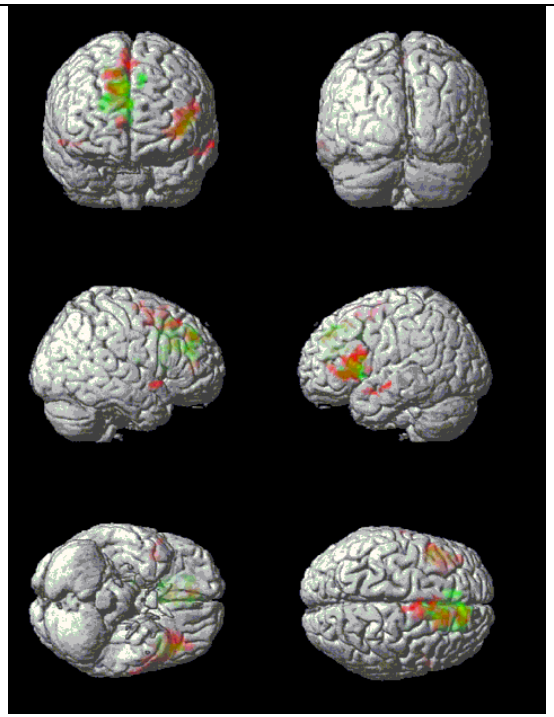
Figure 3.4, Self negative>caps negative (red) and self positive>caps positive (green) contrasts by group

Results are uncorrected for multiple comparisons. Only clusters of voxels with a minimum of 20 voxels are included. P was set at <0.001.

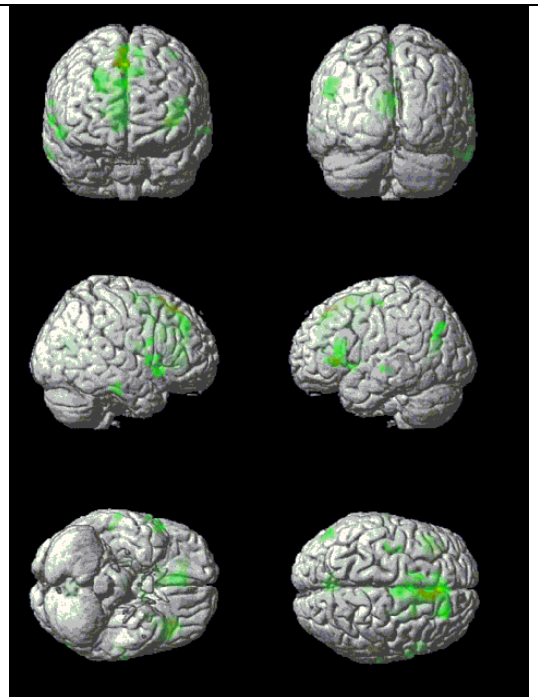
Images are imposed on a sample brain from SPM8 (Friston et al., 2007). Anterior, posterior, lateral, inferior, and superior views are shown.



Control group (n=10) – self negative>caps negative (red) and self positive-caps positive



Depressed group(n=10) – self negative>caps negative (red) and self positive-caps positive



Post-therapy group (n=10) – self negative>caps negative (red) and self positive>caps positive (green)

(green)	(green)	

ANOVAs were carried out to investigate which of the between group differences reached statistical significance. In the self negative>caps negative contrast the depressed group showed significantly greater BOLD signal change in the caudate, areas of the frontal lobe (including the superior frontal gyrus (BA6, BA8), medial areas (BA5), and the inferior frontal gyrus (BA13, BA45)), the vACC (BA24), the dorsal anterior cingulate cortex (dACC; BA32) and the insula (BA13) (please see Appendix 10 for more details). There were no areas of greater significance in the control group than the depressed group in the self negative>caps negative contrast. These findings partially support hypothesis five. Specifically, differences between the control group and the depressed group were observed in the vACC, but not in the mPFC.

In the self positive>caps positive contrast the depressed group showed significantly greater BOLD signal change than the control group in the frontal cortex (superior frontal gyrus (BA6), medial frontal gyrus (BA6), middle frontal gyrus (BA6), precentral gyrus (BA4)), the dorsal anterior cingulate cortex (BA32), the thalamus, the superior occipital gyrus (BA19) and the cuneus (BA18; Appendix 10). There were no areas of greater BOLD signal change in the control group than the depressed group in this contrast. These findings do not support hypothesis five as the areas showing significant differences between the control group and the depressed group do not correspond to the hypothesis.

3.3.7. Hypothesis six.

The sixth hypothesis was that previously depressed participants who have received psychological intervention for depression would show normalisation of neural activity in the self negative>caps negative contrast, but not in the self positive>caps positive contrast. Given previous results, this would meant that in the self-negative>caps negative contrast participant who had recovered from depression following psychological intervention would show less BOLD response than the depressed group in the caudate, areas of the frontal lobe (including the superior frontal gyrus (BA6, BA8), medial areas (BA5), and the inferior frontal gyrus (BA13, BA45)), the vACC (BA24), the dorsal anterior cingulate cortex (dACC; BA32) and the insula (BA13).

A T test was carried out across the post-therapy group to investigate the self-negative>caps negative contrast (Figure 3.4, final cell). A similar pattern of BOLD response was observed in the post-therapy group to that observed in the control group. Specifically, in contrast to the depressed group, there were limited areas of significant BOLD response. This is in keeping with the normalisation predicted by hypothesis six.

In order to investigate whether these differences were statistically significant, an ANOVA was carried out. In the self negative>caps negative contrast the depressed group contrast showed significantly greater BOLD signal change than the post-therapy

group in the caudate, the superior frontal gyrus (BA6, BA), the anterior cingulate cortex (BA24, BA32)the posterior cingulate cortex (BA7) and the precuneus (BA7) (please see Appendix 10 for further details). There were no areas of significantly greater BOLD signal change in the post-therapy group compared to the depressed group. These findings are in keeping with hypothesis six as they can be interpreted as normalisation following psychological intervention.

A T test was carried out across the post-therapy group to find areas of significant BOLD signal change associated with the self-positive>caps positive contrast. The results of the self positive>caps-positive T test in the post-therapy group (Figure 3.4, final cell) are not indicative of normalisation. This is in keeping with hypothesis six.

An ANOVA was carried out to investigate significant differences between the post-therapy group and the other two groups in the self positive>caps positive contrast. The post-therapy group showed greater BOLD signal change than the control group in areas including the frontal cortex (superior frontal gyrus (BA6), medial frontal gyrus (BA8), middle frontal gyrus (BA37), inferior frontal gyrus (BA37)), the anterior cingulate cortex (BA24, BA32), the posterior cingulate cortex (BA31), the claustrum, the insula (BA13) and the culmen (please see Appendix 10 for more details). There were no areas of significantly different BOLD signal change in either group when the post-therapy group and the depressed group were compared. This is not suggestive of normalisation and is therefore in keeping with hypothesis six.

3.4. Summary of Results (Table 3.4)

Hypothesis	Supported?	Details
1	Partially	In the self>other contrast differences were observed in the posterior cingulate cortex (PCC), but not in the medial prefrontal cortex (mPFC), the dorsolateral prefrontal cortex (dlPFC), or the supragenual anterior cingulate cortex (SACC). Differences were also observed in diffuse areas of the fronto-parietal cortex.
2	No	The post-therapy group did not show normalisation in the self>other contrast.
3	No	During negative self-referential processing differences between the control and the depressed groups were only evident in areas not predicted by the hypothesis. During positive self-referential processing there were no significant differences between the control and depressed groups.
4	Partially	During negative self-referential processing the post-therapy group showed a reduction in neural activation. However, this resulted in fewer areas of significant neural activation than the control group. Prior results precluded the possibility of normalisation during positive self-referential processing.
5	Partially	In the self negative>caps negative contrast differences were observed in the ventral anterior cingulate cortex (vACC) and in other areas not predicted by the hypothesis. In the self-positive>caps-positive contrast differences were observed only in areas not predicted by the hypothesis.
6	Yes	Normalisation occurred in the self negative>caps negative contrast but not in the the self positive>caps positive contrast.

4. Discussion

4.1. Overview

The study investigated whether talking therapy and recovery from depression would be associated with a normalisation of neural activation during self-referential processing. The aim was to aid the development of a more holistic understanding of depression by studying it in the context of a cognitive process (self-referential processing) and physiological evidence (neural activation). This is important in the context of disparate bodies of physiological, social and psychological evidence and the dominance of physiological research. The inclusion of participants who had received medication as well as a talking therapy meant that the changes in neural activation that were identified may relate to talking therapy, medication or, more generally, to recovery from depression.

Self-referential processing is an important area for research in depression because of the centrality of the self in models of depression (e.g. Hollon & Beck, 1979) and mindfulness based models of depression (e.g. Segal et al., 2002). There is persuasive evidence of the efficacy of therapeutic techniques such as CBT and mindfulness based cognitive therapy (e.g. Hans & Hiller, 2013; Piet & Hougaard, 2011), both of which are associated with changing unhelpful cognition about the self. There is a new and growing body of research investigating the physiological correlates of psychological therapy on patterns of neural activation. Such research is important in the move towards a more holistic understanding of the aetiology and maintenance

of depression, helping to support a more sophisticated appreciation of the interaction that must exist between the biological, psychological and social.

In the current study, fMRI provided a means of recording physiological changes relative to self-referential processing. The neural activation of 14 participants, who had recovered from depression after receiving psychological intervention, was compared to that of 10 currently depressed participants and 12 non-depressed participants using ANOVA. Self-referential processing was measured by subtracting neural activation associated with judgements about whether a trait described the Queen of England from activation associated with judgements about whether a trait described themselves. Similar paradigms have been successfully used in previous literature (Kelley et al., 2002; Sarsam, 2006; Sarsam et al., 2013). In order to investigate the between group effects of valence further, ANOVAs were performed on the self negative>other negative and self positive>other positive contrasts. Previous research (Lemogne et al., 2010; Yoshimura et al., 2013) has investigated the effects of intervention for depression on self-referential processing by subtracting semantic or graphical conditions. To align the current study with this prior literature the self negative>caps negative and self positive>caps positive contrasts were also investigated.

The findings suggest that recovery from depression following talking therapy was not associated with normalisation of neural activation during general self-referential processing. However, when neural activation during negative self-

referential processing was considered separately, there was a normalisation of previously high levels of activation. One possible interpretation is that the talking therapy that participants received specifically changed negative self-referent cognition, but did not change the tendency to engage in atypical self-referential cognition in general.

The findings bring together physiological and cognitive evidence in the context of depression. Investigating the neural correlates of self-referential processing involves conceptualising the physiological and cognitive as two sides of the same coin, whereas frequently they are viewed as separate. This moves towards a more unified model of depression and adds to another layer of evidence supporting psychological models of depression. Currently research on depression is dominated by physiological research. In such an environment evidence of the physiological correlates of psychological processes may be particularly convincing as to the strength of psychological theories.

This discussion will address each of the study's hypotheses in turn. It will then discuss the results relating to general self-referential processing and valence-specific (positive and negative) self referential processing. The implications of the results will be explored in terms of clinical practice, cognitive models of depression and future research. Finally limitations with the research will be discussed.

4.2. Hypotheses

When considering the neural areas mentioned in the hypotheses it is important to note that the literature on which they were based (Lemogne 2010; Yoshimura et al., 2010, 2013) used different contrasts to investigate self-referential processing and this may have affected the results. Additionally, Lemogne et al. (2010) restricted the analysis of the fMRI images to the prefrontal cortex and Yoshimura et al. (2013) report only valence specific results.

Hypothesis one: In the self>other contrast differences in BOLD signal change will be observed between control participants and depressed participants in the medial prefrontal cortex (mPFC), the dorsolateral prefrontal cortex (dlPFC), the posterior cingulate cortex (PCC), and the supragenual anterior cingulate cortex SACC).

In the self>other contrast there were significant differences between the control group and the depressed group. Specifically, greater BOLD signal change was observed in the control group compared to the depressed group in the PCC. This is in line with the hypothesis. However, in contrast to the hypothesis, no significant differences in BOLD signal change were observed between the groups in the dlPFC, mPFC or the SACC.

Greater BOLD signal change in the control group compared to the depressed group was also found in the precuneus, the precentral gyrus and the postcentral gyrus. This had not been predicted by the hypothesis.

Hypothesis two: In the self>other contrast previously depressed participants who have received psychological intervention for depression will show normalisation of BOLD signal change, that is, their patterns of neural activity during self-referential processing will become more similar to that of control participants.

In the self>other contrast an ANOVA did not find evidence of normalisation in the PCC in the post-therapy group. Neither was there evidence of normalisation in the precuneus, the precentral gyrus or the postcentral gyrus. BOLD response during self-referential processing in the post-therapy group was similar to that of the depressed group. This is not in line with what was hypothesised as it was expected that recovery from depression would be associated with a normalisation of neural functioning during self-referential processing.

Hypothesis three: During positive and negative self-referential processing there will be differences between control participants and depressed participants in the ventral anterior cingulate cortex (VACC; BA24), the mPFC and, during positive self-referential processing only, the superior temporal cortex.

In the valence-specific self-referential contrasts, no differences were observed between the control group and the depressed group in the VACC (BA24), mPFC or the superior temporal cortex. Therefore, these findings were not in line with the hypothesis, which was based on the findings of Yoshimura and colleagues (2013).

The depressed group showed greater BOLD signal change than the control group for negative self-referential processing in the left inferior frontal gyrus, left middle frontal gyrus, left insula, and precentral gyrus. These areas of difference had not been predicted by the hypothesis. There were no significant differences between the control group and the depressed group relating to positive self-referential processing.

Hypothesis four: Previously depressed participants who have received psychological intervention for depression will show normalisation of neural activity during negative self-referential processing, but not during positive self-referential processing.

The post-therapy group showed reduced BOLD signal change during negative self-referential processing in the left inferior frontal gyrus, the left middle frontal gyrus, the left insula, the left dlPFC and the precentral gyrus. However, the magnitude of these reductions meant that the post-therapy group had significantly lower neural activation than the control group. The areas in which the control group and the depressed group differed were not predicted by the hypothesis.

As there were no significant differences between the control group and the depressed group relating to positive self-referential processing there could be no normalisation. This is in line with the hypothesis. There were significant differences in BOLD signal change between the post-therapy group and the control and the

depressed groups. These included greater BOLD signal change in the post-therapy group in the posterior lobe of the cerebellum (declive).

Hypothesis five: In the contrast involving a graphical condition, such as judging whether a word is in capital letters, (e.g. self negative>caps negative or self positive>caps positive) the control group and the depressed group will show different patterns of BOLD response in the vACC (BA24), mPFC and, for positive words, the superior temporal cortex.

In the self negative>caps negative contrast the depressed group showed greater BOLD signal change than the control group in the VACC (BA24), but not the mPFC. The depressed group also showed greater BOLD signal change in diffuse areas of the frontal cortex, the caudate, the SACC, the PCC and the insula.

In the self positive>caps positive contrast the depressed group showed greater activation than the control group in the dorsal ACC, as well as in diffuse areas of the frontal cortex, the thalamus, claustrum, fusifrom gyrus, middle temporal gyrus, occipital gyrus and cuneus. No areas of greater BOLD signal change were found in the mPFC or the superior temporal cortex.

Hypothesis six: Previously depressed participants who have received psychological intervention for depression will show normalisation of neural activity in the self negative>caps negative contrast, but not in the self positive>caps positive contrast.

The post-therapy group showed normalisation of BOLD signal change in the self negative>caps negative contrast in the vACC (BA24, diffuse areas of the frontal cortex, the caudate, the SACC, the PCC and the insula. The normalisation is in line with the hypothesis.

The post-therapy group did not show normalisation of BOLD signal change during self positive>caps positive contrast, rather, in some areas, they became more different from the control group. Specifically, in some of the areas where the depressed group had shown greater BOLD signal change than the control group the post-therapy group showed even greater BOLD signal change.

In keeping with the hypothesis, there was normalisation in the negative condition, but not in the positive condition. However, some of the neural areas implicated were different from those predicted by the hypothesis.

4.3. Contextualising in Current Literature

4.3.1. General self-referential processing.

The main analysis involved subtracting localised neural activity during other-referential processing from activity levels during self-referential processing. The preliminary results seem to support earlier work (d'Argembeau et al., 2007; Craik et al., 1999; Gutchess et al., 2007; Heatherton et al., 2006; Kelley et al., 2002; Sarsam, Parkes, Roberts, Reid & Kinderman, 2013; Yoshimura 2010; 2013) as they indicate

areas of self-specific activation. Further, self-specific processing was associated with increased activation in the anterior and posterior cingulate cortex, which is in keeping with previous work (Craik et al., 1999; d'Argembeau et al., 2007; Gutchess et al., 2007; Heatherton et al., 2006; Kelley et al., 2007). In the control group self-specific processing was associated with increased activation in the precuneus. This is in keeping with d'Argembeau et al. (2007).

Unlike d'Argembeau et al. (2007), Gutchess et al. (2007), Heatherton et al. (2006), Kelley et al. (2002), Sarsam et al. (2013), and Yoshimura et al., (2010; 2013) the current study did not find increased activity in the medial prefrontal cortex (mPFC) during self-referential processing. This is particularly surprising as the mPFC is the neural area most frequently associated with self-referential processing (e.g. d'Argembeau et al., 2007; Gutchess et al., 2007; Heatherton et al., 2006; Kelley et al., 2002; Sarsam et al., 2013; Yoshimura 2010; 2013).

Schmitz and colleagues (2004) use self>other and a self>semantic contrasts to investigate self-referential processing. The self>semantic contrast resulted in significant BOLD signal change in the mPFC as well as in the retrosplenial cortex, thalamus and medial orbital cortex. The self>other contrast resulted in no significant mPFC BOLD signal change. The authors report that mPFC activation is not specific to self-referential processing but also present during other-referential processing; as such it cannot be isolated by the self>other contrast. Their findings are in keeping with those of Craik and colleagues (1999) and with the current study. However,

d'Argembeau and colleagues (2007), Gutchess and colleagues (2007), Heatherton and colleagues (2006), Kelley and colleagues (2002) and Sarsam and colleagues (2013) also use a self>other contrast and report significant mPFC activity during self-referent cognition. The reason for these contradictory findings remains unclear, although Schmitz and colleagues (2004) have suggested that political ideology (if political figures are used as the other) or how well participants know the "other" may play a role.

Significant neural activation in the insula was associated with self-referential processing. This association has been previously reported by Modinos, Ormel and Aleman (2009). Additionally, Longe and colleagues (2010) report activation in the insula during self-reassurance. Along with the anterior cingulate cortex, the insula is part of the "salience network" (Menon & Uddin, 2010; Palaniyappan & Liddle, 2012), which is important in considering salience to self, and is therefore likely to have been active during this task. There is also evidence that the insula plays a role in switching attention between internally focussed and externally focussed neural networks (Menon & Uddin, 2010). This task may have been particularly important in the current study design as it reflects the nature of the contrast in question; participants were asked to switch their attention between themselves (internal) and the queen (external). The event-related design meant that the frequency of these switches in attention, and possibly therefore the cognitive demand, was increased.

The control group showed more widespread neural activation in relation to self-referential processing than the depressed group. These differences reached significance in the precuneus, precentral gyrus, inferior frontal gyrus, postcentral gyrus, superior temporal gyrus and the posterior cingulate gyrus. There were no areas of significantly higher neural activation in the depressed group compared to the control group. In contrast, Sarsam and colleagues (2013) report that the more widespread self-related neural activity in the control group did not reach significance, but find higher self-related neural activity in the depressed group than the control group in the mPFC and the anterior cingulate cortex.

The apparently greater self-related neural activity in control participants may be misleading. Higher results from the self-referential>other-referential contrast may relate to ongoing self-referential processing during other-referential task. This is because the self-referential>other-referential contrast is defined as neural activation during self-referential processing minus neural activation during other-referential processing. This interpretation is in keeping with the "impaired disengagement model" of depression (Koster, Lissnyder, Derakshan & De Raedt, 2011), which suggests that people with depression have difficulty switching attention away from ruminative self-referent cognitions. Sheline and colleagues (2009) provide further physiological support for this model by presenting evidence that people with depression do not show a reduction of default mode network (DMN) activation during the completion of tasks.

Lemogne and colleagues (2009) report higher levels of mPFC and dlPFC self-related activation in depressed participants than control participants and Yoshimura and colleagues (2010) report higher levels of mPFC and ACC self-related activation in depressed participants than control participants. This study differed in that there were no areas of greater activation in the depressed group than the control group. It is of note that Lemogne and colleagues' (2009) analysis involved only the prefrontal area. This restriction of the analysis increased the power of the design and may have meant that more subtle differences reached significance. It may be that Yoshimura and colleagues' (2010) findings relate only to valence-specific self-referential processing (that is positive self-referential processing or negative self-referential processing) as the authors report only valence-specific contrasts.

When positive and negative self-referential processing were considered together the post-therapy group's patterns of neural activation were more similar to that of the depressed group than that of the control group. This is in contrast to the study's hypothesis. However, normalisation may have been masked because the positive, negative and neutral words were considered together.

4.3.2. Negative self-referential processing.

In this study negative self-referential processing was investigated through the self negative>other negative contrast. The areas of greater negative self-related neural activation in the depressed group than the control group (left inferior frontal gyrus, left middle frontal gyrus, left insula, and left precentral gyrus) do not correspond to the

hypothesis, which was based on the findings of Yoshimura and colleagues (2013). However, the contrast differed from that used by Yoshimura and colleagues (2013), which subtracted semantic and letter processing conditions from the self condition and may therefore have isolated less specific cognitive processes.

The areas that showed greater BOLD signal change during negative self-referential processing in the depressed group compared to the control group have previously been identified as important in self-referential processing. In a review of imaging studies investigating self-referential processing Morin and Michau (2007) report that 55.9% have significant findings in the left inferior frontal gyrus. The left middle frontal gyrus (Heatherton et al., 2006; Lemogne et al., 2010; Platek, Keenan, Gallup & Mohamed, 2004) and insula (Modinos et al., 2009) have also been implicated in self-referential processing. Interestingly, Lemogne and colleagues (2010) report that the left precentral gyrus shows greater activation during negative self-referential processing, whilst the right precentral gyrus shows greater activation during positive self-referential processing, which is in keeping with the results of this study.

The self negative>caps negative contrast used in this study, which is closer to the contrast used by Yoshimura and colleagues (2013) did result in greater ACC activation in the depressed group than the control group. This is in keeping with Yoshimura and colleagues' (2013) findings. This contrast was less specific than the self negative>other negative contrast; it may not have isolated self-referential

cognition, but rather a broader span of cognitive processes including autobiographical memory, language processing and inferential processing. This may account for the more widespread neural activation with which it was associated. In addition to the ACC, significantly greater activation in the depressed group than the control group was observed in a number of areas that have previously been linked to self-referential processing. These were the paracentral lobule (Seger, Stone & Keenan, 2004), the superior frontal gyrus (Goldberg, Harel & Malach, 2006), the inferior frontal gyrus (Morin & Michau, 2007), the posterior cingulate cortex (Heatherton et al., 2006) and the insula (Modinos et al., 2009).

The post-therapy group showed normalisation of neural activation during negative self-referential processing. Specifically, areas that had greater BOLD signal change in depressed participants compared to control participants had reduced BOLD signal change in the post-therapy group. This is in keeping with the findings of Lemogne and colleagues (2010) and Yoshimura and colleagues (2013) as well as research relating to emotional processing (Fu et al., 2004, 2008; Ritchey et al., 2010). There is strong evidence that on recovery from depression there is a normalisation of the negative dysfunctional attitudes that are associated with depression (Ingram, Miranda & Segal, 1998). The normalisation of the post-therapy group's neural activation during negative self-referential processing is in keeping with this finding.

4.3.3. Positive self-referential processing.

The current study did not find significant differences in neural activation between the control group and the depressed group during positive self-referential processing, which was investigated by the self positive>other positive contrast. However, the self positive>caps positive contrast, which was more similar to the contrast used by Yoshimura and colleagues (2013) revealed greater activation in the depressed group than the control group in the dorsal ACC, premotor cortex, supplementary motor area, precentral gyrus, thalamus, claustrum, fusifrom gyrus, middle temporal gyrus, occipital gyrus and cuneus. The ACC (Craik et al., 1999; d'Argembeau et al., 2007; Gutchess et al., 2007; Heatherton et al., 2006; Kelley et al., 2007) and the middle temporal gyrus (d'Argembeau et al., 2005) have been associated with self-referential processing.

It should be considered that the contrast in which differences between the control group and the depressed group were apparent (self positive>caps positive) is not self-specific. It is likely that the contrast results in residual language, memory and inferential processing and it may be these processes that underlie the differences between the control group and the depressed group.

Goldin and colleagues (2009) use a block design fMRI study to investigate self-referential processing before and after mindfulness based stress reduction. The study involves a self positive>caps positive contrast. Although the study involved participants with social anxiety disorder, the results are in keeping with the current study as the authors report significant BOLD signal change in the premotor cortex,

thalamus, fusiform gyrus, occipital gyrus and cuneus associated with the self positive>caps positive contrast.

In the self positive>caps positive contrast neural activation in the post-therapy group did not show normalisation, but instead the hyper-activation associated with depression seemed to increase following psychological intervention for depression. This was particularly true in the ACC and the mPFC (BA8). Both of which have been implicated in self-referential processing (d'Argembeau et al., 2007; Gutchess et al., 2007; Heatherton et al., 2006; Kelley et al., 2002; Sarsam et al., 2013; and Yoshimura et al., 2010; 2013). However, as this contrast is not self-specific, it may be that the differences reported relate to changes in memory or language processing or inferential processing following talking therapy and recovery from depression.

The self positive>other positive contrast is likely to isolate self-specific processing more effectively than the self positive>caps positive contrast. Unlike the self positive>caps positive contrast, the self positive>other positive contrast did not result in increased BOLD response in the post-therapy group compared to the depressed group. Rather, there were some areas that showed greater BOLD response in the control group and some areas that showed greater BOLD response in the depressed group. The limited availability of research in this area makes these findings difficult to interpret. It suggests that changes in self-specific processing relating to talking therapies and recovery from depression may be relatively complex. However,

the inclusion of people who had received medication in the post-therapy group means that some or all of the changes may relate to medication.

4.4. Implications

4.4.1. Implications for clinical practice.

The research facilitates the integration of knowledge from different professional perspectives (medically oriented and psychologically oriented). This is likely to be particularly helpful in the context of a research base that has been described as "fragmented" (Kecmanovic, 2011). Integration of previously fragmented knowledge has the potential to positively affect communication within multi-disciplinary teams and enable more evidence-based clinical decision making. Additionally, the holistic approach has the potential to help avoid situations where clients are given multiple conflicting explanations for their difficulties, thus reducing client confusion.

The results of this thesis add to evidence that some neural activation patterns change on recovery from depression. This evidence supports a move away from biological determinism towards a framework that includes physiological evidence, but offers more hope for recovery. Additionally, research that explores the neural correlates of psychological processes after therapy may aid the development of more effective psychological interventions.

It is possible that the ongoing atypical neural activation during self-referential processing in the post-therapy group was due to ongoing depressive symptoms, possibly following a course of therapy that was too short. This is in keeping with reports from the IAPT Therapists that a key barrier to recruitment was that many people that they discharged had not recovered. However, given that the BDI II (Beck et al., 1996) scores of the control group and the post-therapy group were comparable, it may be that the BDI II (Beck et al., 1996) lacks the sensitivity to detect some potentially problematic cognitive processes associated with depression (for example self esteem or self efficacy).

It was not possible to investigate the impact of the number of the therapy sessions that participants had received as many participants could not provide this information. Additionally, it was not possible to obtain pre- and post-therapy psychometric data for the post-therapy participants who were recruited via the university web-site. This possibility is therefore worthy of exploration in future research as it would have important implications for the delivery of therapy and for the choice of measures used to monitor therapeutic outcome.

4.4.2. Implications for theory.

The results elucidate some of the relationships between physiological and psychological elements of depression. Traditional bio-psycho-social models typically suggest that permanent biological factors affect cognition, which, in turn, affects social issues. Functional MRI research frequently necessitates a move away from these models; it investigates the biological and the cognitive as inseparable parts of the same process. Furthermore, the current research represents an attempt to investigate the cognitive and physiological effects of a psychosocial intervention, which draws into question the assumption that atypical biological factors associated with depression should be treated with biological interventions. However, confounding variables mean that the changes observed may relate to medication or to recovery from depression.

Traditional cognitive models of depression emphasise the centrality of dysfunctional negative cognitions about the self, the world and the future in the development and maintenance of depression. The difference between the neural activation patterns of control participants and depressed participants during negative self-referential processing, and the normalisation the neural activation patterns in the post-therapy group, provide physiological support for this aspect of the model. However, the results do not allow exploration of whether there is a causal or correlational relationship between negative cognitions about the self and depression.

The post-therapy group showed more significant areas of neural activation in the self positive>caps positive contrast than the control group. It is possible that this

reflected a recently acquired, and somewhat effortful, habit of selectively attending to and recalling positive information about the self. This may have resulted from specific or general factors of talking therapy, or, due to confounding variables, from antidepressant medication or simply from recovery from depression. From this perspective the atypical activation during positive self-referential processing could be seen as a (possibly temporary) protective factor.

An alternative interpretation is that the high levels of neural activation in the self positive>caps positive contrast in the post-therapy group represent an ongoing tendency to engage in self-referent cognition. It is possible that this would be a risk factor for future episodes of depression.

4.4.3. Implications for future research.

Given the relatively small sample size, replication of this study using larger sample sizes would be very useful. Recruitment difficulties meant that the inclusion and exclusion criteria for the current study were relaxed and consequently confounding variables were introduced, specifically participants had received talking therapy of various types and some participants had also received medication. These factors had a direct impact on the conclusions that could be drawn from the results. Research that avoided confounding variables in this was would be valuable.

Research that compared people who had followed different paths to recovery (talking therapy, medication or no intervention) would allow exploration of the relationship between the changes in BOLD response and recovery. It may be that the

changes in BOLD response that were observed are the physiological manifestation of cognitive changes that directly underlie recovery. In this case similar changes would be expected irrespective of whether the person had recovered with talking therapy, with medication, or without any kind of intervention, and the type of medication and modality of therapy would be unimportant. It is also possible that the changes that were observed in this study relate specifically to talking therapy and other types of intervention lead to a different pattern of changes. Similarly, different types of talking therapy may result in different patterns of change. For example, Mindfulness Based Cognitive Therapy specifically targets self-related ruminative cognition and avoids practising focussing attention elsewhere. It is possible that such an approach would bring about a particulary marked change in neural activation during self-referential processing. Research investigating these issues would further our understanding of the mechanisms of recovery and may aid in the development of more effective interventions.

Within the current study participants were only scanned once. This avoided the confounding effects of changes in neural activation associated with multiple scans. However, there would be significant advantages associated scanning over the course of depression and before depression develops. Such an approach might elucidate specific patterns of self-related neural activation that increases the risk of developing depression and the extent to which any atypical patterns of activation persist following recovery from depression.

It would be particularly useful to investigate the impact of ongoing high levels of neural activation during positive self-referential processing, specifically whether it has protective effects or is predictive of relapse. Similarly, it would be useful to explore whether high levels of neural activation during positive self-referential processing in people who have never been depressed predicts subsequent development of a major depressive episode.

In keeping with Sheline and colleagues (2009), the author has suggested that the apparently lower levels of neural activation during self-referential processing in the depressed and post-therapy group compared to the control group may have resulted from difficulty directing attention away from the self towards other tasks. It would be useful to explore this possibility more fully in future research. It would also be useful to explore the extent to which group differences were due to different activation during other-referential processing rather than self-referential processing. The reliance of fMRI studies on contrasts, for example self>other, made this issue difficult to explore in the current study.

All of the participants for this study were from a western individualist society. However there is evidence that people with more collectivist understandings of self have different patterns of neural activation during self-referential processing (Chiao, 2009). Therefore, the results may not have cross-cultural relevance. Future research could explore the applicability of current models of depression to people from

collectivist societies and cross-cultural differences in neural activation during self-referential processing.

Researchers have reported an association between certain genetic polymorphisms and rumination (Beevers, Wells & McGeary, 2009; Clasen, Wells, Knopik, McGeary & Beevers, 2011), which seems to be mediated by adverse experiences (Clasen et al., 2011). Such research draws together genetic and psychological models of depression, whilst highlighting the impact of trauma. It would be useful to use fMRI to investigate self-referential processing in people with these polymorphisms and to investigate the effects of psychological therapies in this context.

There is some evidence that a failure to reduce DMN activity during cognitive tasks is associated with increased creativity (Takeuchi et al., 2011). Exploration of these findings in relation to depression and low mood may elucidate potential adaptive features of this cognitive style.

4.5. Summary

This research provides evidence of ongoing atypical neural activation in previously depressed people who have had psychological intervention for depression. However, the contrasts investigating negative self-referential processing suggest that

recovery from depression is associated with a normalisation of previously high levels of neural activation during negative self-referential processing.

Ongoing atypical activation during self-referential processing has not been reported before. In this respect it is an interesting result, but it is possible that considering both positive and negative self-referential processing together resulted in a misleading confounding of variables. That is, normalisation of neural activation during negative self-referential processing may have been masked by increased neural activation during positive self-referential processing.

It is also possible that ongoing atypical neural activation during self-referential processing relates to participants receiving insufficient therapy. This would have implications for the way that therapy is delivered within the NHS and for the measures that are used to assess whether a client has recovered.

The normalisation of neural activation during negative self-referential processing on recovery from depression is in keeping with other literature and fits with cognitive theories of depression. Such theories emphasise the importance of negative cognition about the self in the development and maintenance of depression.

Physical evidence of normalisation may offer more hope for recovery as it emphasises the plasticity of neural functioning. An association between this normalisation and talking therapy moves away from the assumption that physical

factors should be treated with medication. However, the inclusion of participants who had received antidepressant medication means that there is a possibility that observed differences between the depressed group and the post-therapy group are related to medication.

4.6. Limitations

Impact of recruitment difficulties: The study had ongoing problems with recruitment, which meant that completion of the project was delayed and the original research design was subject to two substantial amendments. Unfortunately, some of the strategies used introduced confounding variables that may have affected the results of the research. The recruitment approach that was adopted represents an attempt to balance the potentially conflicting demands of maximising recruitment and maintaining a high quality of data.

Despite the strategies that were put in place, recruitment was a significant difficulty with this research. Relying on Therapists to recruit seemed to be particularly problematic; whereas advertising on the University of Liverpool intranet for participants who had completed a course of therapy for depression was relatively effective. An alternative approach would have been to pay Therapists for recruitment, although the ethics of doing so would have to be carefully considered.

Salmon and colleagues (2007) suggest that the lack of value that is placed on research is a key factor predicting GPs' decisions to participate in research. From this perspective strategies that fail to address this issue are unlikely to be successful. Although the hypothesis explored in this study has important clinical implications these may not have been immediately relevant to the Therapists in the study. It may be that in an environment in which research is seen as less important than clinical work the current project was seen as particularly lacking in value.

Sample size: A major limitation of this study is the relatively small sample size. This means that the study may not have the power to detect some significant differences between groups.

Single time-point design: The study design was changed from a repeated measure design to a single time-point design due to ethical and feasibility considerations. However, the original repeated-measures design would have been more statistically powerful and results may have been more compelling.

Sample matching: Due to the small sample size and missing data, it was not possible to match participants on years in education. Matching by age and gender was done where possible, but small sample size meant that it was not possible to perfectly match groups based on these criteria. This may have introduced confounding variables, as little is known about the effect of gender, educational level and age on self-referential processing in depression.

Variety of therapeutic modalities: The post-intervention sample was a naturalistic sample collected from a local IAPT service and from a student community population. Participants had accessed a range of non-manualised psychological interventions, including CBT, cognitive behavioural techniques and counselling. This has the advantage of meaning that the results have local relevance. It also means, however, that the individual role of specific therapies has not been explored. For example, it may be that as self-referential processing is particularly relevant to the cognitive model of depression, and CBT specifically aims to change beliefs about the self, CBT has a greater impact than counselling on neural activation during self-referential processing. The small sample size meant that analysis by modality sub-group could not be carried out.

Length of time since last therapy session: The amended recruitment strategy meant that most participants recruited through advertisements on the university web-site were not recruited as soon as their therapy ended. The shortest length of time since the last therapy session was one month and the longest length of time was two years. This introduced a potentially confounding variable that may have affected the results.

Length of therapy: Participants who were recruited via the university intranet did not know how many sessions of therapy they had received. This information may have been useful in considering the results.

Antidepressant use: three of the post-therapy group were using antidepressant medication and six had used antidepressant medication in the past, but were no longer using it. This has the advantage of meaning that the sample was reasonably representative, as antidepressant medication is typically prescribed for moderate to severe depression as recommended by NICE (NICE, 2009), but introduces a confounding variable that may have affected the results.

The depressed group were drawn from an earlier study with slightly different exclusion criteria. In contrast to the post-therapy group they were not using antidepressants or any other psychoactive medication. As a result the observed differences between the depressed group and the control group are more readily associated with depression. However, it should also be considered that depressed people who avoid antidepressants are a self-selecting group and may not be representative of the population from which they are drawn.

Culture: The linguistic base of the cognitive activation paradigm meant that participants were excluded if they did not speak English as a first language. This means that the results cannot be generalised to people from other backgrounds.

A famous person rather than a well known friend or relative was chosen as the subject for the other-referential condition. This was done to avoid the confounding effects that might be introduced if participants had relatively small social circles or

difficulties within relationships. It was felt to be particularly important as people with depression are more likely to have difficulties with relationships. However, it is important to note that the participants may have differing attitudes towards the queen and this may have affected their neural activation patterns. Unfortunately, participants' attitudes towards the Queen were not recorded and so cannot be included as a variable.

Screening for reading ability: Participants' reading ability was screened to ensure that they reached a minimal standard of reading. Participants in the post-therapy group were required to read the first item of the BDI II with no mistakes. Participants in the control and depressed groups, which were collected by Sarsam et al. (2013), were required to read the first column of the NART with less than six mistakes. This change in methodology was introduced to reduce the time required for the pre-scan screen. Neither measure resulted in participants being excluded. However, the use of different methodologies may have meant that participants were included in the post-therapy group who would not have been included in the control or depressed groups, or vice-versa.

4.7. Conclusions

Taken in the context of the recently published work of Yoshimura and colleagues (2013) it is likely that some of the differences in the neural activation patterns of depressed participants and controls normalise on recovery from depression. This moves away from biological determinism and therefore offers more hope for

recovery. However, despite a normalisation of BDI II (Beck et al., 1996) scores, some previously depressed participants had ongoing atypical neural activation during self-referential processing. There are a number of possible explanations for this. For example, it may be that the intervention participants received did not adequately address self-referential rumination, the intervention may have been too short, or the BDI II (Beck et al., 1996) may lack the sensitivity to measure certain aspects of depression.

The research represents an attempt to promote the unification of different types of evidence (cognitive and physiological) in the context of competing models of depression. There is mounting physiological evidence (Lemogne, 2009; 2010, Sarsam et al., 2013; Yoshimura et al., 2010; 2013) supporting the importance of self-referential processing in depression, which is in keeping with psychological models. The presentation of physiological evidence for psychological models is important. It may be particularly persuasive for researchers and clinicians who tend to favour biological evidence. It also helps specify relationships within the bio-psycho-social model, specifically whether they are causal, correlational, or different aspects of the same process.

It would be useful to explore possible differences in neural activity changes between different types of therapy. This would help shed light on some of the mechanisms of therapy and greatly add to research around the non-specific effects of therapy. Similarly, it would be useful to investigate the neural activation patterns of

people who recover from depression without medication or psychological therapy. Such research would lead to a better understanding of psychological well-being.

5. References

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: Author.

Anderson, N.H. (1968). Likableness ratings of 555 personality-trait words. *Journal of Personality and Social Psychology*. 9: 272–279.

Andrews-Hanna, J. R., Reidler, J. S., Sepulcre, J., Poulin, R. & Buckner, R. L. (2010). The functional-anatomic fractionation of the brain's default network. *Neuron*, 65, 550-562.

Barrash, J., Tranel, D. & Anderson, S. W. (2000). Acquired personality disturbances associated with bilateral damage to the ventromedial prefrontal region. *Developmental Neuropsychology*, 18, 355-381.

Bechara, A., Damasio, H., Tranel, D. & Anderson, S.W. (1998). Dissociation of working memory from decision making within the human prefrontal cortex. *Journal of Neuroscience*, 18, 428–437.

Beck, A.T. (1967). *Depression: Clinical, experimental and theoretical aspects.* London: Staples Press.

Beck, A.T. (1971). Cognition, affect and psychopathology. *Archives of General Psychiatry*, 24, 495-500.

Beck, A.T. (1976). *Cognitive Therapy and the Emotional Disorders.* Oxford, England: International Universities Press.

Beck, A. T., Steer, R. A., Ball, R. & Ranieri, W. (1996). Comparison of Beck Depression Inventories –IA and –II in psychiatric outpatients. *Journal of Personality Assessment*, 67, 588-597.

Beck, A.T., Steer, R.A., & Brown, G.K. (1996). *Manual for the Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation.

Beevers, C.G., Wells, T.T. & McGeary, J. E. (2009). The BDNF Val66Met polymorphism is associated with rumination in health adults. *Emotion*, 9, 579-584.

Bentall, R. (2004). *Madness explained: Psychosis and Human Nature.* Penguin: London.

Berger, J.L & Addis, M.E. (2012). The effects of gender, diagnostic labels and causal theories on willingness to report symptoms of depression. *Journal of Social and Clinical Psychology*, 31, 439-457.

Bhagwagar, Z., Whale, R. & Cowen, P. J. (2002). State and trait abnormalities in serotonin function in major depression. *British Journal of Psychiatry*, 180, 24-28.

Bifulco, A., Moran, P. M. & Ball, C. Bernazzani, O. (2001). Adult attachment style. I: Its relationship to clinical depression. *Social Psychiatry and Psychiatric Epidemiology*, 37, 50-59.

Blackburn, I.M., Eunson, K.M. & Bishop, S. (1986). A two-year naturalistic follow-up of depressed patients treated with cognitive therapy, pharmacotherapy and a combination of both. *Journal of Affective Disorders*, 10, 67-75.

Bower, P., Wallace, P., Ward, E., Graffy, J., Miller, J., Delaney, B. & Kinmonth, A.L. (2009). Improving recruitment to health research in primary care. *Family Practice*, 26, 391–397.

Brewin, C.R., (1996). Theoretical foundations of cognitive-behaviour therapy for anxiety and depression. *Annual Review of Psychology*, 47, 33-57.

Brody, A.L., Saxena, S, Schwartz, JM, Stoessel, PW, Maidment, K, Phelps, ME, & Baxter Jr, LR. (1998). FDG-PET predictors of response to behavioural therapy and pharmacotherapy in obsessive complsive disorder. *Psychiatry Research: Neuroimaging Section*, 84, 1-6.

Broome, MR, Matthiasson, P, Fusar-Poli, P, Wooley, JB, Johns, LC, Tabraham, P, Bramon, E, Valmaggia, L, Williams, SCR, Brammer, MJ, Chitnis, X & McGuire, PK. (2009). Neural correlates of executive function and working memory in the 'at-risk mental state'. *The British Journal of Psychiatry*, 194, 25-33.

Butler, A.C., Chapman, J.E., Forman, E.M. & Beck, A.T. (2006). The empirical status of cognitive behavioural therapy: a review of meta-analyses. *Clinical Psychology Review*, 26, 17-31.

Carter, R. (1998). *Mapping the Mind.* London, Phoenix.

Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A. & Poulton, R. (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*, 301, 386-389.

Chen, M.C., Hamilton, J.P. & Gottlib, I.H. (2010). Decreased Hippocampal Volume in Healthy Girls at Risk of Depression. *Archives of General Psychiatry*, 67, 270-276.

Chen, C.-H., Ridler, K., Suckling, J., Williams, S., Fu, C.H.Y., Merlo-Pich, E. & Bullmore, E. (2007). Brain imaging correlates of depressive symptom severity and predictors of symptom improvement after antidepressant treatment. *Biological Psychiatry*, 62, 404-414.

Chiao, J.Y. (2009). Cultural neuroscience: A once and future discipline. *Progress in Brain Research*, 178, 287-304.

Clasen, P.C., Wells, T.T., Knopik, V.S., McGeary, J.E. & Beevers, C.G. (2011). 5-HTTLPR and BDNF Val66Met polymorphisms moderate effects of stress on rumination. *Genes, Brain and Behaviour*, 10, 740-746.

Cohen, C. I. (1993). The biomedicalization of psychiatry: A critical overview. *Community Mental Health Journal*, 29, 509-521.

Cohen, S. & Wills, T.A. (1985). Stress, social support, and the buffering hypothesis. *Psychological Bulletin*, 98, 310–357.

Cole, J., Costafreda, S.G., McGuffin, P. & Fu, C.H.Y. (2011). Hippocampal atrophy in first episode depression: A meta-analysis of magnetic resonance imaging studies. *Journal of Affective Disorders*, 134, 483-487.

Craik, F.I.M., Moroz, T.M., Moscovitch, M., Stuss, D.T., Winocur, G., Tulving, E. And Kapur, S. (1999). In search of the self: A positron emission tomography study. *Psychological Science*, 10, 26-34.

Cuijpers, P., Geraedts, A.S., van Oppen, P., Andersson, G., Markowitz, J.C. & van Straten, A. (2011). Interpersonal Psychotherapy for depression: A meta-analysis. *American Journal of Psychiatry*, 168, 581-592.

Dannlowski, U, Ohrmann, P, Bauer, J, Kugel, H, Arolt, V, Heindel, W, Kersting, A, Baune, BT & Suslow, T. (2007). Amygdala reactivity to masked negative faces is assosciated with automatic judgemental bias in major depression: a 2 T fMRI study. *Journal of Psychiatry and Neuroscience*, 32, 423-429.

D'Argembeau, A, Ruby, P, Collette, F, Degueldre, C, Balteau, E, Luxen, A, Maquet, P & Salmon, E. (2007). Distinct regions of the medial prefrontal cortex are

associated with self-referential processing and perspective taking. *Journal of Cognitive Neuroscience*, 19, 935-944.

Davidson, R.J., Lewis, D.A., Alloy, L.B., Amaral, D.G., Bush, G., Cohen, J.D., et al. (2002). Neural and behavioural substrates of mood and mood regulation. *Biological Psychiatry*, 52, 478–502.

Davis, M. & Whalen, P. J. (2001). The amydala: vigilance and emotion. *Molecular Psychiatry*, 6, 13-34.

Decety, J. & Jackson, P.L. (2004). The functional architecture of human empathy. *Behavioral and cognitive neuroscience*, 3, 71-100.

Derogatis, L. R. (1994). *SCL-90-R: Administration, Scoring and Procedures Manual*. Minneapolis, National Computer Systems, Inc.

Dozois, D.J.A. & Dobson, K.S. (2001). Information processing and cognitive organization in unipolar depression: Specificity and comorbidity issues. *Journal of Abnormal Psychology*, 110, 236-246.

Dougherty, D & Rauch SL. (1997). Neuroimaging and neurobiological models of depression. *Harvard Review of Psychiatry*, 5, 138-159.

Drevets, W.C., Videen, T.O., Price, J.L., et al.(1992). A functional anatomical study of unipolar depression. *Journal of Neuroscience*, 12, 3628-3641.

Dunn, B.D., Stefaovitch, I., Buchan, K., Lawrence, A.D. & Dalgleish, T. (2009). A reduction in positive self-judgment bias is uniquely related to the anhedonic symptoms of depression. *Behaviour Research and Therapy,* 47, 374-381.

Edwards, V.J., Holden, G.W., Felitti, V.J. & Anda, R.F. (2003). Relationship between multiple forms of childhood maltreatment and adult mental health in community respondents: results from the adverse childhood experiences study. *American Journal of Psychiatry*, 160, 1453–1460.

Engels, G.L. (1977). The need for a new medical model: A challenge for biomedicine. *Science,* 196(4286), 129-136.

Etkin, A, Pittenger, C, Polan, HJ & Kandel, ER. (2005). Towards a neurobiology of psychotherapy: Basic science and clinical applications. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 17, 145-158.

Evans, M.D., Hollon, S.D., DeRubeis, R.J., Piasecki, J.M, Grove, W.M.., Garvey, M.J. & Tuason, V.B. (1992). Differential relapse following cognitive therapy and pharmacotherapy for depression. *Archives of General Psychiatry*, 49, 802-808.

Farb, N.A.S., Anderson, A.K., Mayberg, H., Bean, J., McKeon, D. & Segal, Z.V. (2010). Minding one's emotions: mindfulness training alters the neural expression of sadness. *Emotion*, 10, 25-33.

Farb, N.A.S., Segal, Z.V., Mayberg, H., Bean, J., McKeon, D., Fatima, Z. & Anderson, A.K. (2007). Attending to the present: mindfulness meditation reveals distinct neural modes of self-reference. *SCAN*, 2, 313-322.

Felitti, V.J., Anda, R.F., Nordenberg, D., Williamson, D.F., Spitz, A.M., Edwards, V., Koss, M.P. & Marks, J.S. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *American Journal of Preventative Medicine*, 14, 245–258.

Finger, E.C., Marsh, A.A., Mitchell, D.G., Reid, M. E., Sims, C., Budhani, S., ... Blair, J. R. (2008). Abnormal ventromedial prefrontal cortex function in children with psychopathic traits during reversal learning. *Archives of General Psychiatry*, 65, 586–594.

First, M.B., Spitzer, R.L, Gibbon, M. & Williams, J.B.W. (1996). *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version* (SCID-CV). Washington, D.C.: American Psychiatric Press, Inc.

Foong, J., Symms, M. R., Barker, G., Mier, M., Woerman, F., Miller, D. H. & Ron, M. A. (2001). Neuropathological abnormalities in schizophrenia: Evidence from magnetisation transfer imaging. *Brain*, 5, 882-892.

Formisano, E., Di Salle, F. & Goebel R. (2006). Fundamentals of data analysis methods in fMRI. In *Advanced Image Processing in Magnetic*

Resonance Imaging. L. Landini, V. Positano & M.F. Santarelli (Eds.) CRC Press: Boca Raton, Florida.

Forstmann, B. U.; Van den Wildenberg, W. P.M. & Ridderinkhof, R. K. (2008). Neural Mechanisms, Temporal Dynamics, and Individual Differences in Interference Control. *Journal of Cognitive Neuroscience,* 20, 1854-1865.

Foy, R., Parry, J., Duggan, A., Delaney, B., Wilson, S., Lewin-van den Broek, N.Th., Lassen, A, Vickers, L. & Myres, P. (2003). How evidence based are recruitment strategies to randomised controlled trial in primary care? Experience from seven studies. *Family Practice*, 20, 83-92.

Frewen, P. A., Dozois, D.J.A. & Lanius, R.A. (2008). Neuroimaging studies of psychological interventions for mood and anxiety disorders: Empirical and methodological review. *Clinical Psychology Review*, 28, 228-246.

Friston, K.J., Ashburner, J.T., Kiebel, S., Nichols, T.E. & Penny, W.D. (2007). *Statistical Parametric Mapping: The Analysis of Functional Brain Images.* Elsevier/Academic Press: Amsterdam.

Frith, U. & Frith, C.D. (2003). Development & neurophysiology of mentalizing. *Philosophical Transactions of the Royal Society*, 358(1431), 459-473.

Fu, CHY, Williams, SCR, Cleare, AJ, Brammer, MJ, Walsh, ND, Kim, J, Andrew, CM, Pich, EM, Williams, PM, Suckling, J & Bullmore, ER. (2004).

Attenuation of the neural response to sad faces in major depression in antidepressant treatment. *Archives of General Psychiatry*, 61, 877-889.

Fu, CHY, Williams, SCR, Cleare, AJ, Scott, J, Mitterschiffthaler, MT, Walsh, ND, Donaldson, C, Suckling, J, Andrew, C, Steiner, H & Murray, RM. (2008). Neural responses to sad facial expressions in major depression following cognitive behavioural therapy. *Biological Psychiatry*, 64, 505-512.

Fulford, K.W.M & Colombo, A. (2004). Six Models of Mental Disorder: A Study Combining Linguistic-Analytic and Empirical Methods. *Philosophy, Psychiatry and Psychology*, 11, 129-144.

Fuster, J.M. (2008). *The prefrontal cortex.* Academic Press: London.

Gabbard, G.O. A neurobiologically informed perspective on psychotherapy. *The British Journal of Psychiatry*, 177, 117-122.

Gallagher, H.L. & Frith, C.D. (2003). Functional imaging of "theory of mind." *Trends in Cognitive Sciences*, 7, 77-83.

Gemar, M.C., Segal, .ZV., Sagrati, S. & Kennedy, S.J. (2001). Mood-induced changes on the Implicit Association Test in recovered depressed patients. *Journal of Abnormal. Psychology.* 110: 282–89.

Ghaemi, N. S. (2009). The rise and fall of the biopsychosocial model. *British Journal of Psychiatry*, 195, 3-4.

Gillihan, S. J., & Farah, M. J. (2005). Is self special? A critical review of evidence from experimental psychology and cognitive neuroscience. *Psychological Bulletin*, 131, 76–97.

Goebel, R., Esposito, F. & Formisano, E. (2006). Analysis of FIAC data with BrainVoyager QX: From single-subject to cortically aligned group GLM analysis and self-organizing group ICA. *Human Brain Mapping*, 27, 392–401.

Goldapple, K., Segal, Z., Garson, C., Lau, M., Bieling, P., Kennedy, S. & Mayberg, H. (2004). Modulation of cortical-limbic pathways in major depression. *Archives of General Psychiatry*, 61, 34-41.

Goldberg, I.I., Harel, M. & Malach, R. (2007). When the brain loses its self: Prefrontal inactivation during sensorimotor processing. *Neuron*, 50, 329-339.

Goldin, P., Ralel, W. & Gross, J. (2009). Mindfulness Meditation Training and Self-Referential Processing in Social Anxiety Disorder: Behavioral and Neural Effects. *Journal of Cognitive Psychotherapy*, 23, 242-257.

Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R., Friston, K. J. & Frackowiak, R. S. J. (2001). A voxel based morphometric study of ageing in 465 normal adult human brains. *NeuroImage*, 14, 21-36.

Greicius, MD, Flores, BH, Menon, V, Glover, GH, Solvason, HB, Kenna, H, Reiss, AL & Schatzberg, AF. (2007). Resting-state functional connectivity in major depression: Abnormally increased contributions from subgenal cingulate cortex and thalamus. *Biological Psychiatry*, 62(5), 429-437.

Greicius, M.D., Flores, B.H., Menon, V., Glover, G.H., Solvason, H.B., Kenna, H., Reiss, A.L. & Schatzberg, A.F. (2007). Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. *Biological Psychiatry*, 62, 429-437.

Greicius, M.D., Supekar, K., Memon, V. & Dougherty, R.F. (2009). Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cerebral Cortex*, 19, 72-78.

Gusnard, DA, Akbudak, E, Shulman, GL & Raichle, ME. (2001). Medial prefrontal cortex and self-referential mental activity: Relation to a default mode of brain function. *Proceedings of the National Academy of Sciences USA*, 98, 4259-4264.

Gutchess, A. H., Kensinger, E. A. & Schachter, D. L. (2007). Aging, self-referencing, and medial prefrontal cortex. *Social Neuroscience*, 2, 117-133.

Halbreich, U., Alarcon, RD., Calil, H., Douki, S., Gaszner, P., Jadresic, E. ... Trivedi, JK. (2007). Culturally sensitive complaints of depressions and anxieties in women. *Journal of Affective Disorders*, 102, 159-176.

Hammen, C. (2005). Stress and depression. *Annual Review of Clinical Psychology*, 1, 293-319.

Hamilton, M. (1980). Rating depressive patients. *Journal of Clinical Psychiatry*. 41, 21-24.

Hans, E. & Hiller, W. (2013). Effectiveness of and dropout from outpatient cognitive behavioral therapy for adult unipolar depression: A meta-analysis of nonrandomized effectiveness studies. *Journal of Consulting and Clinical Psychology*, 81, 75-88.

Heatherton, T. F., Wyland, C. L., Macrae, C. N., Demos, K. E., Denny, B. T. & Kelley, W. M. (2006). Medial prefrontal cortex activity differentiates self from close others. *Social Cognitive and Affective Neuroscience*, 1, 18-25.

Heim, C. & Binder, E. B. (2012). Current research trends in early life stress and depression: Review of human studies on sensitive periods, gene-environment interactions, and epigenetics. *Experimental Neurology*, 233, 102-111.

Heim, C., Newport, D. J., Miller, A. H. & Nemeroff, C.B. (2000). Long-term neuroendocrine effects of childhood maltreatment. *JAMA*, 284, 2321.

Heim, C., Newport, D.J., Bonsall, R., Miller, A.H. & Nemeroff, C.B. (2001). Altered pituitary-adrenal axis responses to provocative challenge tests in adult

survivors of sexual abuse. *American Journal of Psychiatry,* 158, 575-581.

Heim, C., Newport, D.J., Mletzko, T., Miller, A.H. & Nemeroff, C.B. (2008). The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology,* 33, 693-710.

Hogard, N, Darwent, G, Capener, D, Wilkinson, ID & Griffiths, PD. (2009). The high incidence and bioethics of findings on magnetic resonance brain imaging of normal volunteers for neuroscience research. *Journal of Medical Ethics,* 35, 194-199.

Hollon, S.D. & Beck, A.T. (1979). Cognitive therapy of depression. In P.E. Kendall & S.S. Hollon (Eds.) *Cognitive-Behavioral Interventions: Theory, research, procedures,* (pp. 153-203). New York: Academic Press.

Ingram, R.E., Miranda, J. & Segal, Z.V. (1998). *Cognitive Vulnerability to Depression.* New York: Guildford Press.

Ishikawa, Y., Meyer, J. S., Tanahashi, N., Hata, T., Veles, M., Fann, W. E., ... Rogers, R. L. (1986). Abstinence improves cerebral perfusion and brain volume in alcoholic neurotoxicity without Wernicke-Korsakoff syndrome. *Journal of Cerebral Blood Flow and Metabolism,* 6, 86-94.

Johnson, S. C., Baxter, L. C., Wilder, L. S., Pipe, J. G., Heiserman, J. E. & Prigatano, G. P. (2002). Neural correlates of self-reflection. *Brain*, 125, 1808-1814.

Just, N. & Alloy, L.B. (1997). The response styles theory of depression: Tests and an extension of the theory. *Journal of Abnormal Psychology*, 106, 221-229.

Karg, K., Burmeister, M., Shedden, K. & Sen, S. (2011). The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation. *Archives of General Psychiatry*, 68, 444-454.

Kecmanovic, D. (2011). Conceptual discord on psychiatry: origin, implications and failed attempts to resolve it. *Psychiatria Danubine*, 23, 210-222.

Keedwell, P. A., Drapier, D., Surgladze, S., Giampietro, V., Brammer, M. & Phillips. M. (2010). Subgenual cingulate and visual cortex responses to sad faces predict clinical outcome during antidepressant treatment for depression. *Journal of Affective Disorders*, 120, 120-125.

Kelley, W. M., Macrae, C. N., Wyland, C. L., Caglar, S., Inati, S. & Heatherton, T. F. (2002). Finding the self? An event-related fMRI study. *Journal of Cognitive Neuroscience*, 14, 785-794.

Kendall, P.C. & Bemis, K. (1983). Thought and action in psychotherapy: the cognitive behavioural approaches. In M. Hersen, A. E. Kazdin & A.S.

Bellack (Eds.), *The Clinical Psychology Handbook*, (565-592). New York: Pergamon.

Kennedy, SH, Javanmard, M & Vaccarino, FJ. (1997). A review of functional neuroimaging in mood disorders: Positron emission tomography and depression. *Canadian Journal of Psychiatry*, 42, 467-475.

Kennedy, SH, Konarski, JZ, Segal, ZV, Lau, MA, Bieling, PJ, McIntyre, RS & Mayberg, HS. (2007). Differences in brain glucose metabolism between responders to CBT and venlafaxine in a 16-week randomized control trial. *American Journal of Psychiatry*, 164, 778-788.

Kessler, R.C., Nelson, C., McGonagle, K.A., Liu, J., Schwartz, M. & Blazer, D. G. (1996). Comorbidity of DSM-III-R major depressive disorder in the general population: results from the US National Comorbidity Survey. *British Journal of Psychiatry*, 168(suppl 30): 17–30.

Kim, K. H., Relkin, N. R., Lee, K. & Hirch, J. (1997). Distinct cortical areas associated with native and second languages. *Nature*, 388, 171-174.

Kinderman, P., Schwannauer, M., Pontin, E. & Tai, S. (2013). Psychological processes mediate the impact of familial risk, social circumstances and life events on mental health. *PLOS ONE*, 8(10): e76564. doi:10.1371/journal.pone.0076564.

Kinderman, P, Sellwood, W. & Tai, S. (2008). Policy implications of a psychological model of mental disorder. *Journal of Mental Health*, 17, 93-103.

Kinderman, P. (2005). A psychological model of mental disorder. *Harvard Review of Psychiatry*, 13, 206-217.

Koenigs, M. & Grafman, J. (2009). The functional neuroanatomy of depression: Distinct roles for ventromedial and dorsolateral prefrontal cortex. *Behavioural Brain Research*, 201, 239-243.

Koster, E.H.W., De Lissnyder, E., Derakshan, N. & De Raedt, R. (2011). Understanding depressive rumination from a cognitive science perspective: The impaired disengagement hypothesis. *Clinical Psychology Review*, 31, 138-145.

Kuehlwein, K.T. (2002). The cognitive treatment of depression. In G. Simos (Ed.) *Cognitive Behaviour Therapy: A guide for the practising clinician*, (pp. 3-48). Hove: Routledge.

Kuyken, W., Byford, S., Taylor, R.S., Watkins, E., Holden, E., White, K. ... Teasdale, J.D. (2008). *Journal of Consulting and Clinical Psychology*, 76, 966-978.

Legrand, D. & Ruby, P. (2009). What is self-specific? Theoretical investigation and critical review of neuroimaging results. *Psychological Review*, 116, 252-282.

Lehto, SM, Tolmunen, T, Joensuu, M, Saarinen, PI, Valkonen-Korhonen, M, Vanninen, R. ... Lehtonen, J. (2008). Changes in midbrain seretonin transporter availability in atypically depressed subjects after one year of psychotherapy. *Progress in Neuro-Psycopharmacology and Biological Psychiatry*, 32, 229-237.

Lemogne, C., le Bastard, G., Mayberg, H, Volle, E, Bergouignan, L, Lehericy, S, ... Fossati, P. (2009). In search of the depressive self: extended medial prefrontal cortex network during self-referential processing in major depression. *SCAN*, 4, 305-312.

Lemogne, C, Mayberg, H, Bergouignan, L, Volle, E, Delaveau, P, Lehericy, S., ... Fossati, P. (2010). Self-referential processing and the prefrontal cortex over the course of depression: A pilot study. *Journal of Affective Disorders*, 124, 196-201.

Lepine, J.P., Gastpar, M., Mendlewicz, J. & Tylee, A. (1997). Depression in the community: The first pan-European study DEPRES. *International Clinical Psychopharmacology*, 12, 19-29.

Levinson, D.F. (2006). The genetics of depression: a review. *Biological Psychiatry*, 60, 84-92.

Linden, DEJ. (2006). How psychotherapy changes the brain - the contribution of functional neuroimaging. *Molecular Psychiatry*, 11, 528-538.

Linden, DEJ. (2008). Brain imaging and psychotherapy: methodological considerations and practical implications. *European Archives of Psychiatry and Clinical Neuroscience*, 258 (Suppl 5), 71-75.

Longe, O., Maritos, F.A., Gilbert, P., Evans, G., Volker, F., Rockliff, H. & Rippoon, G. (2010). Having a word with yourself: Neural correlates of self-criticism and self-reassurance. *NeuroImage*, 49, 1849-1856.

MacQueen, G. M. (2009), Magnetic resonance imaging and prediction of outcome in patients with major depressive disorder. *Journal of Psychiatry and Neuroscience*, 34, 343-9.

Martin, SD, Martin, E, Rai, SS, Richardson, MA & Royall, R. (2001). Brain blood flow changes in depressed patients treated with interpersonal psychotherapy or venlafaxine hydrochloride. *Archives of General Psychiatry*, 58, 641-648.

Mathews, A. & MacLeod, C. (1994). Cognitive approaches to emotion and emotional disorders. *Annual Review of Psychology*, 45, 25–50.

Mathews, A., Ridgeway, V. & Williamson, D.A. (1996). Evidence for attention to threatening stimuli in depression. *Behaviour Research and Therapy*, 34, 695-705.

Mayberg, HS, Brannan, SK, Mahurin, RK, Jerabek, PA, Brickman, JS, Tekell, JL, ... Fox, PT. (1997). Cingulate function in depression: a potential predictor

of treatment response. *Clinical Neuroscience and Neuropathology*, 8, 1057-1061.

McClintock, S. M., Husain, M. M., Greer, T. L. & Cullum, C. M. (2010). Association between depression severity and neurocognitive function in major depressive disorder: A review and synthesis. *Neuropsychology*, 24, 9-34.

McEwen, B.S. (1999). Stress and hippocampal plasticity. *Annual Review of Neuroscience*, 22,105-122.

McRae, K, Ochsner, KN, Mauss, IB, Gabrieli, JJD & Gross, JJ. (2008). Gender differences in emotion regulation: an fMRI study of cognitive reappraisal. *Group Processes and Intergroup Relations*, 11, 143-162.

McCrone, P., Dhanasiri, S., Patel, A., Knapp, M. & Lawton-Smith, S. (2008). *Paying the price: The cost of mental health care in England to 2026.* Kings Fund: London.

Menon, V. & Uddin, L.Q. (2010). Saliency, switching attention and control: a network model of insula function. *Brain Structure and Function*, 214, 655-667.

Modinos, G., Ormel J. & Aleman, A. (2009). Activation of anterior insula during self-reflection. PLoS ONE 4(2), Retrieved from: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0004618.

Moghaddam, B & Homayoun, H. (2008). Divergent plasticity of prefrontal cortex networks. *Neuropsychopharmacology REVIEWS*, 33, 42-55.

Mor, M. & Winquist, J. (2002). Self-focused attention and negative affect: a meta-analysis. *Psychological Bulletin*, 128, 638-662.

Morin, A. & Michaud, J. (2007). Self-awareness and the left inferior frontal gyrus: Inner speech use during self-related processing. *Brain Research Bulletin*, 74, 387-396.

Mugler, J. P. & Brookeman, J. R. (1990). Three-dimensional magnetisation-prepared rapid gradient-echo imaging (3D MP-RAGE). *Magnetic Resonance in Medicine*, 15, 152-157.

Murphy, K. & Garavan, H. (2004). An empirical investigation into the number of subjects required for an event-related fMRI study. *NeuroImage*, 22, 879-885.

Murray, E.A. (2007). The amygdala, reward and emotion. *Trends in Cognitive Sciences*, 11, 489-497.

NCCMH (2010). *Depression: the Treatment and Management of Depression in Adults (Update).* Leicester and London: The British Psychological Society and the Royal College of Psychiatrists.

NICE (2009). *Depression: the Treatment and Management of Depression in Adults. (Update).* NICE clinical guideline 90. Available at www.nice.org.uk/CG90.

Nolen-Hoeksema, S. (2000). Further evidence for the role of psychosocial factors in depression chronicity. *Clinical Psychology Scientific Practice,* 7, 224–227.

Nolen-Hoeksema, S. (1991). Responses to depression and their effects on the duration of depressive episodes. *Journal Abnormal Psychology*, 100, 569–582.

Nolen-Hoeksema, S. & Morrow, J. (1991). A prospective study of depression and posttraumatic stress symptoms after a natural disaster: The 1989 Loma Prieta earthquake. *Journal of Personality and Social Psychology*, 61, 115-121.

Norbury, R., Mackay, C.E., Cowen, P.J., Goodwin, G.M. & Harmer, C.J. (2008). The effects of reboxetine on emotional processing in healthy volunteers: an fMRI study. *Molecular Psychiatry*, 13, 1011-1020.

Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H. & Panksepp, J. (2006). Self-referential processing in our brain - A meta-analysis of imaging studies on the self. *NeuroImage*, 31, 440-457.

Ochsner, K.N., Beer, J.S., Robertson, E.R., Cooper, J.C., Gabrieli, J.D.E., Kihlstrom, J.F. & S'Esposito, M. (2005). The neural correlates of direct and reflected self-knowledge. *NeuroImage*, 28, 797-814.

Ochsner, K. N., Bunge, S. A., Gross, J. J., & Gabrieli, J.D. (2002). Rethinking feelings: an fMRI study of the cognitive regulation of emotion. *Journal of Cognitive Neuroscience*, 14, 1215-1229.

Ongur, D., & Price, J.L. (2000). The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cerebral Cortex*, 10, 206–219.

Palaniyappen, L. & Liddle, P. F. (2012). Does the salience network play a cardinal role in psychosis? An emerging hypothesis of insular dysfunction. *Journal of Psychiatry and Neuroscience*, 37, 17-27.

Patel, M.X., Doku, V. & Tennakoon, L. (2003). Challenges in recruitment of research participants. *Advances in Recruitment of Research Participants*, 9, 229-238.

Patil, T. & Giordano, J. (2011). On the ontological assumptions of the medical model of psychiatry: philosophical considerations and pragmatic tasks. *Philosophy, Ethics and Humanities in Medicine*, 5:3. Retrieved from http://www.biomedcentral.com/content/pdf/1747-5341-5-3.pdf

Penza, K.M., Heim, C. & Nemeroff, C.B. (2003). Neurobiological effects of childhood abuse: implications for the pathophysiology of depression and anxiety. *Archives of Women's Mental Health*, 6, 15-22.

Phan, K. L., Fitzgerald, D. A., Nathan, P. J., Moore, D. J., Uhde, T. W. & Tancer, M. E. (2005). Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. *Biological Psychiatry,* 57, 210-209.

Piet, P. & Hougaard, E. (2011). The effect of mindfulness-based cognitive therapy for prevention of relapse in recurrent major depressive disorder: A systematic review and meta-analysis. *Clinical Psychology Review*, 31, 1032-1040.

Pilgrim, D. (2011). Conference proceedings. Some limitations of the biopsychosocial model. *History and Philosophy of Psychology*, 13, 21-27.

Pilgrim, L. K., Fadili, J., Fletcher, P. & Tyler, L. K. (2002). Overcoming confounds of stimulus blocking: An event-related fMRI design of semantic processing. *NeuroImage*, 16, 713-723.

Platek, S.M., Keenan, J.P., Gallup Jr., G.G. & Mohamed, F.B. (2004). Where am I? The neurological correlates of self and other. *Cognitive Brain Research,* 19, 114-122.

Platek, .S.M., Thomson, J.W. & Gallup, G.G. (2004). An integrated and intermodal self: cross modal self-recognition. *Consciousness and Cognition*. 13, 197-210.

Pruessner, J.C., Baldwin, M.W., Dedovic, K., Renwick, R., Mahani, N.K., Lord, C., ... Lupien, S. (2005). Self-esteem, locus of control, hippocampal volume, and cortisol regulation in young and old adulthood. *NeuroImage*, 28, 815-826.

Raichle, M.E. &. Snyder, AZ. (2007). A default mode of brain function: A brief history of an evolving idea. *Neuroimage*, 37, 1083-1090.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A. & Shulman, G.L. (2001). A default mode of brain function. Proceeding of the National Academy of Sciences USA, 98, 676-682. *Academy of Sciences USA*, 98, 676-682.

Read, J., Bentall, R.P. & Fosse, R. (2009). Time to abandon the bio-bio-bio model of psychosis: Exploring the epigenetic and psychological mechanisms by which adverse life events lead to psychotic symptoms. *Epidemiologia and Psichiatria Sociale*, 18, 299-307.

Rigucci, S., Serafina, G., Pompili, M., Kotzalidis, G. D. & Tatarelli, R. (2010). Anatomical and functional correlates in major depressive disorder: The contribution of neuroimaging studies. *The World Journal of Biological Psychiatry*,11, 165-180.

Ritchey, M., Dolcos, F., Eddington, K.M., Strauman, T.J. & Cabeza, R. (2011). Neural correlates of emotional processing in depression: Changes with cognitive behavioral therapy and predictors of treatment response. *Journal of Psychiatric Research*, 45, 577-587.

Ruby, P. & Decety, J. (2003). What you believe versus what you think they believe: a neuroimaging study of conceptual perspective taking. *European Journal of Neuroscience*, 17, 2475-2480.

Ruby, P. & Decety, J. (2004). How would *you* feel versus how do you think *she* would feel. A neuroimaging study of perspective-taking with social emotions. *Journal of Cognitive Neuroscience*, 16, 988-999.

Rutter, M. (1989). Pathways from childhood to adult life. *Journal of Child Psychology and Psychiatry*, 30, 23-51.

Ross, S., Grant, A., Counsell, C., Gillespie, W., Russell, I. & Prescott, T. (1999). Barriers to participation in randomised controlled trials: A systematic review. *Journal of Clinical Epidemiology*, 52, 1143-1156.

Salmon, P., Peters, S., Rogers, A., Gask, L., Clifford, R., Iredale, W. ... Morriss, R. (2007). Peering through the barriers in GPs' explanations for declining to participate in research: the role of professional autonomy and the economy of time. *Family Practice*, 24, 269–275.

Sarsam, M. (2006). *Self-referential processing in depression: An fMRI study investigating the application of cognitive models of depression to neurofunctional brain activity.* (Doctoral Dissertation), University of Liverpool, England.

Sarsam, M., Parkes, L.M., Roberts, N., Reid, G.S. & Kinderman, P. (2013). The Queen and I: Neural correlates of altered self-related cognitions in major depressive episode. *PLoS ONE* 8(10): e78844. doi:10.1371/journal.pone.0078844

Schacter, D. L. & Buckner, R. L. (1998). Priming the brain. *Neuron,* 20, 185-195.

Schmitz, T.W. Kawahara-Baccus, T.N. & Johnson, S.C. (2004). Metacognitive evaluation, self-relevance and the right pre-frontal cortex. *NeuroImage*, 22, 941-947.

Segal, Z.V., Bieling, P., Young, T., MacQueen, G., Cooke, R., Martin, L. ... Levitan, R.D. (2010). Antidepressant Monotherapy vs Sequential Pharmacotherapy and Mindfulness-Based Cognitive Therapy, or Placebo, for Relapse Prophylaxis in Recurrent Depression. *Archives of General Psychiatry,* 67, 1256-1264.

Segal, Z.V., Williams, J.M.G. & Teasedale, J.D. (2002). *Mindfsulness-based cognitive therapy for depression.* The Guilford Press: New York.

Seger, C.A., Stone, M. & Keenan, J. (2004). Activations during judgements about the self and an other person. *Neuropsychologia*, 42, 1168-1177.

Sharp, T. & Cohen, P.J. (2011). 5-HT and depression: is the glass half full? *Current opinion in pharmacology*, 11, 45-51.

Shea, M.T., Elkin, I., Imber, S., Sotsky, S.M.,Watkins, J.T., Collins, J.F., ...Parloff, M.B. (1992). Course of depressive symptoms over follow up: Findings of the NIMH treatment of depression collaborative research program,. *Archives of General Psychiatry*, 49, 43-50.

Sheline, YI, Barch, DM, Price, JL, Rundle, MM, Vaishnavi, SN, Snyder, AZ, ... Raichle, ME. (2009). The default mode network and self-referential processes in depression. *Proceedings of the National Academy of Sciences USA*, 106, 1942-1947.

Siegle, G.J., Steinhauer, S.R., Thase, M.E., Stenger, V.A. and Carter, C.S. (2002). Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. *Biological Psychiatry*, 2, 693-707.

Siegle, GJ, Carter, CS, & Thase, ME. (2006). Use of fMRI to predict recovery from unipolar depression with cognitive behaviour therapy. *American Journal of Psychiatry*, 163, 735-738.

Simons, A.D., Murphy, G.E., Levine, J.L. & Wetzel, R.D. (1986). Cognitive therapy and pharmacotherapy for depression: Sustained improvement over one year. *Archives of General Psychiatry*, 43, 43-50.

Singleton, SS. (2001). Depression and quality of life: a patient's perspective. *Journal of Clinical Psychiatry,* 62, 26:22.

Sirotion, YB & Das, A. (2009). Anticipatory haemodynamic signals in sensory cortex not predicted by local neuronal activity. *Nature*, 457, 475-480.

Statt, D. A. (2003). "reductionism" *A Students Dictionary of Psychology.* Psychology Press: East Sussex.

Steer, R. A., Ball, R., Ranierei, W. & Beck, A. T. (1997). Further evidence for the construct validity of the Beck Depression Inventory – II with psychiatric patients. *Psychological Reports*, 80, 443-436.

Stuss, D.T., Gallup Jr, G.G. & Alexander, M.P. (2001). The frontal lobes are necessary for "theory of mind." *Brain*, 124, 279-286.

Talairach, J. & Tournoux, P. (1988). *Co-planar Stereotaxic Atlas of the Human Brain: 3-Dimensional Proportional System - an Approach to Cerebral Imaging*. Thieme Medical Publishers: New York.

Teasdale, J.D., Segal, Z.V. Williams, J., Mark, G., Ridgeway, V.A., Soulsby, J.M. & Lau, M.A. (2000). Prevention of relapse/recurrence in major depression

by mindfulness-based cognitive therapy. *Journal of Consulting and Clinical Psychology*, 68, 615-623.

Thesen, S. (2000). Prospective acquisition correction for head motion with image-based tracking for real-time fMRI. *Magnetic Resonance in Medicine,* 44, 457-465.

Thirion, B., Pinel, P., Mériaux, S., Rocheb, A., Dehaenec, S. & Polineb, J.-B. (2007). Analysis of a large fMRI cohort: Statistical and methodological issues for group analyses. *NeuroImage,* 35, 105-120.

Uddin, L, Iacoboni, M, Lange, C & Keenan, JP. (2007). The self and social cognition: the role of cortical midline structures and mirror neurons. *TRENDS in Cognitive Neurosciences*, 11, 153-157.

Vogeley, K. & Gallagher, S. 2011. Self in the brain. In S. Gallagher (ed.), *Oxford Handbook of the Self,* pp. 111-136. Oxford: Oxford University Press.

Vul, E., Harris, C., Winkielman, P. & Pashler, H. (2009). Puzzlingly high correlations in fMRI studies of emotion, personality, and social cognition. *Perspectives on Psychological Science*, 4, 274-291.

Wall, M. (2011). Which fMRI analysis software (SPM, BrainVoyager, FSL)? In *Computing for Psychologists*. Retrieved 12 May 2012, from http://computingforpsychologists.files.wordpress.com/2011/05/m-wall_fmri_software_slides.pdf.

Way, B.M., Cresswell, J.D., Eisenberger, N.I. & Lieberman, M.D. (2010). Dispositional mindfullness and depressive symptomology: Correlations with limbic and self-referential neural activity during rest. *Emotion*, 10, 12-24.

Waraich, P., Goldner, E.M., Sorners, J.M. & Hsu, L. (2004). Prevalence and incidence studies of mood disorders: A systematic review of the literature. *Canadian Journal of Psychiatry*, 49, 124-138.

Wells, K.B., Sturm, R., Sherbourne, C.D. & Meredith, L.S., (1996). *Caring for depression.* Boston: Harvard University Press.

Williams, JMG. (1984). Cognitive-behaviour therapy for depression: Problems and perspectives. *British Journal of Psychiatry*, 145, 254-262.

Wykes, T, Brammer, M, Mellers, J, Bray, P, Reeder, C, Williams, C & Corner, J. (2002). Effects on the brain of a psychological treatment: cognitive remediation therapy. *British Journal of Psychiatry*, 181, 144-152.

Yoshimura, S., Okamoto, Y., Onoda, K., Matsunaga, M., Ueda, K., Suzuki, S. & Shigetoyamawaki. (2010). Rostral anterior cingulate cortex activity mediates the relationship between the depressive symptoms and the medial prefrontal cortex activity. *Journal of Affective Disorders*, 122, 76–85.

Yoshimura, S., Okamoto, Y., Onoda, K., Matsunaga,M., Okada, G., Kunisato, Y., ... Yamawaki, S. (2013). Cognitive behavioral therapy for depression changes medial prefrontal and ventral anterior cingulate cortex activity associated with self-referential processing. *Social Cognitive and Affective Neuroscience.*
Available: http://www.ncbi.nlm.nih.gov/pubmed/23327934. Accessed 2013 Sept 26.

Zald, D. H., Mattson, D. L. & Pardo, J. V. (2002). Brain activity in ventromedial prefrontal cortex correlates with individual differences in negative affect. *Proceeding of the National Academy of Science USA*, 99, 2540-2544.

6. Appendices

Appendix 1

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk. Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering Letter		15 March 2010
REC application	1	11 March 2010
Protocol	1.3	12 December 2009
Investigator CV		16 March 2010
Participant Information Sheet	1	15 January 2010
Participant Consent Form	1	23 January 2010
Letter of invitation to participant	1	16 March 2010
Letter from Sponsor		17 March 2010
Referees or other scientific critique report		26 October 2009
Summary/Synopsis	1	16 March 2010
Advertisement	1	16 March 2010
Investigator CV		16 March 2010
Referees or other scientific critique report		26 October 2009
Letter from funder		23 November 2009

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

10/WNo03/17	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

T.A. Biggs.

Professor Alex Carson
Chair

E-mail: tracy.biggs@wales.nhs.uk

Email: Tracy.Hughes4@wales.nhs.uk

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

"After ethical review – guidance for researchers

Copy to:

Professor Peter Kinderman
School of PCBS, Whelan Building
Quadrangle, Brownlow Hill
Liverpool
L69 3GB

Sarah Fletcher
Legal Services Forsight Building
Liverpool University
Liverpool
L69 3GL

Ms Irene Penney
Knowsley PCT Research & Development
Moorgate Point
Moorgate Road
Knowlsley Industrial Estate
L33 7XW

North Wales Research Ethics Committee (Central & East)

Attendance at Committee meeting on 07 April 2010

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mrs Krystyna Bates	Senior Nurse - Paediatrics	Yes	
Mrs Celia Blomeley	Lay member	Yes	
Professor Alex Carson	Lay member	No	
Dr Kath Clarke	Lead Nurse	No	
Dr John Clifford	Consultant Psychiatrist	Yes	
Reverend Kathy Collins	Chaplain /Lay Member	Yes	
Dr John Delieu	Anatomist & DI for HTA Licence	No	
Miss Joy Hickman	Consultant Orthodontist	No	
Dr Peter Hobson	Principal Healthcare Scientist (Research)	Yes	
Mr John Hughes	Coroner / Lay Member	Yes	
Ms Alison Ledward	Lay Member	Yes	
Mr Philip Richards	Associate Specialist - Surgery	No	
Mrs Elaine Roberts	Antimicrobial Pharmacist	Yes	
Mr Gary Slegg	Research Psychologist	No	
Mr Trevor Smith	Clinical Effectiveness Manager	Yes	
Dr David Southern	Consultant Anaesthetist	Yes	
Miss Eunice Vincent	Lay Member	Yes	
Dr Anthony White	Consultant Physician in Medicine for the Elderly	Yes	
Dr Diane Williamson	Consultant Dermatologist	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Ms Tracy Hughes	Research Ethics Committee Co-ordinator

Appendix 2

NISCHR

Gwasanaeth Moeseg Ymchwil | RES | Research Ethics Service

North Wales REC (Central & East)
G1/G2 Croesnewydd Hall
Croesnewydd Road
Wrexham Technology Park
Wrexham LL13 7YP

Telephone : 01978 726377

E-mail : tracy.biggs@wales.nhs.uk

Website : www.nres.nhs.uk

06 June 2013

Mrs Debbie Watson
Whelan Building, Quadrangle
Brownlow Hill
Liverpool
L69 3GB

Dear Mrs Watson

Study title:	**Self-referential Processing following CBT for Depression: An fMRI study**
REC reference:	**10/WNo03/17**
Protocol number:	**UoL000576**
Amendment number:	**3**
Amendment date:	**27 April 2013**
IRAS project ID:	**35135**

The above amendment was reviewed at the meeting of the Sub-Committee held on 05 June 2013.

Ethical Opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Participant Information Sheet	4	27 April 2013
Protocol	4	11 May 2013
Notice of Substantial Amendment (non-CTIMPs)	3	27 April 2013
Covering Letter		29 May 2013
Web page information		
Advertisement	1	

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

10/WNo03/17:	**Please quote this number on all correspondence**

Yours sincerely

T. A. Biggs.

Professor Alex Carson
Chair

E-mail: tracy.biggs@wales.nhs.uk

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Mr Michael Davis, Knowsley Intergrated Provider Services 5 Boroughs Partnership NHS FT*
Lindsay Carter, University of Liverpool

North Wales REC (Central and East)

Attendance at Sub-Committee of the REC meeting on 05 June 2013

Name	*Profession*	*Capacity*
Professor Alex Carson Chair	Associate Dean (Research)	Lay
Dr Kath Clarke	Deputy Associate Chief of Staff, Nursing	Expert
Reverend Kathy Collins	Chaplain /Lay Member	Lay Plus
Mr Philip Richards	Associate Specialist - Surgery	Expert

Also in attendance:

Name	*Position (or reason for attending)*
Mrs Tracy Biggs	Research Ethics Committee Co-ordinator

Appendix 3

THE UNIVERSITY of LIVERPOOL

MARIARC

Mersey Care NHS
NHS Trust

PSYCHOLOGICAL THEORY, BRAIN ACTIVITY AND DEPRESSION
Information for potential participants

About the study:

Psychological theories suggest that depression comes about because of the way people think and feel about themselves and the world. This can be influenced by negative life events, childhood trauma, feeling hopeless about the future, or many other things.

The study wants to investigate how psychological theory fits in with what actually goes on in our brains when we think about things while depressed. This will help to show why psychological therapies are so successful in treating depression.

The study is taking place through the University of Liverpool Department of Clinical Psychology and Merseycare NHS Trust. It has the approval of the Liverpool Research Ethics Committee (ref 05/Q1505/10).

Who we are looking for:

We would like to recruit participants who are depressed and ***not taking any anti-depressant medication***. Participants should also:

- Be between 18 and 65
- Be right handed
- Speak English as their first language
- Have no history of alcohol or substance misuse
- Have no other (major) mental health difficulties aside from depression (anxiety or panic attacks are very common with depression so this would be acceptable – please call if you are unsure)
- Have no history of brain injury, epilepsy, stroke or dementia
- Have not been born at a weight below 1.5kg, or more than 8 weeks premature.
- Have no internal metal: pins, plates, pacemakers etc (fillings are fine)

If you do not meet these criteria, unfortunately you will not be able to take part.

The study will require three to four hours of your time (a morning or an afternoon). You will receive £25 to cover your travel expenses and your time (it would be your responsibility to declare this for inland revenue purposes).

What will it involve?

- A meeting with the researcher to take down some of your details and fill in some questionnaires about your mood. This will take approximately ninety minutes.
- Going for a Magnetic Resonance Imaging (MRI) brain scan at the University of Liverpool. You will be screened by a MRI nurse who will take your blood pressure and ask some safety questions. While in the scanner, you will be asked to answer some very simple questions to investigate the activity in your brain while thinking about certain things. The scan itself will take no longer than 45 minutes, but we ask people to allow about ninety minutes for the whole process.
- **You are free to withdraw from the study at any point. Your information will not be used without your express permission.**

Who will have access to your information?

All your information would be kept confidential at all times, except under very particular circumstances when it may be important to inform your GP. This would be in the very rare possibility that:

- The researcher identifies a significant risk of harm to yourself or other people.
- Something of concern is uncovered in the MRI scan (less than 1 in a thousand).
- **The research team will never release any information without discussing this with you first.**

The study may be monitored or audited by the Merseycare Governance Committee to ensure that everything has proceeded in a satisfactory manner. Again, your details would remain confidential in this case.

Common questions answered

1. **What is it like in the scanner?**

The MRI Scan is rather noisy but it causes no harm or long-term effects. There are no harmful rays or X-rays – the scanner uses magnetic fields. Some people may experience slight feelings of claustrophobia in the scanner but most people find it quite relaxing. You will be able to hear and speak to the radiographers throughout the scan and you will also have a panic button to press. **If you do feel uncomfortable you will be able to notify us and we will remove you from the scanner straight away.**

2. **What if the scan shows something abnormal?**

The investigators are not trained in diagnosis and these scans are not designed to find abnormalities, so neither the investigator nor the University of Liverpool would be responsible for failure to find abnormalities in your scan. However, if anything of concern should be discovered, the consultant neuro-radiologist at the Walton Centre for Neurology would be informed and asked to report on the scan. If any abnormality is confirmed, the neuro-radiologist would speak with you in person. With your consent, a letter would then be sent to your General Practitioner.

The decision as to whether to proceed with further examinations or treatment lies solely with you and your General Practitioner. The investigator, the neuro-radiologist and the University of Liverpool are not responsible for any examination or treatment that you undertake based upon these findings. Because the images collected in this study are not a proper clinical 'series', they will not be made available for diagnostic purposes.

3. ***What if the clinical interview shows something unexpected?***

The clinical interview will ask you simple questions about your mood and day to day life. It would be very unusual for this to show anything that you are not already aware of, such as anxiety, depression, chronic pain or drinking problems.

In the unlikely case that this does occur, a letter would be sent to your General Practitioner **with your permission**. The only time someone's information would NEED to be passed on is in the highly unlikely event that they expressed a significant risk of harm to themselves or other people.

4. **Can I see the scan?**

If you wish to have a still picture of your scan as a souvenir, this can be arranged and sent to you free of charge.

If you are interested in finding out more, please call:

0151 794 7264

between 9am and 8pm, Monday to Saturday, to speak to a researcher.
Or email ***may.sarsam@liverpool.ac.uk***

Thank you for your time and your interest.

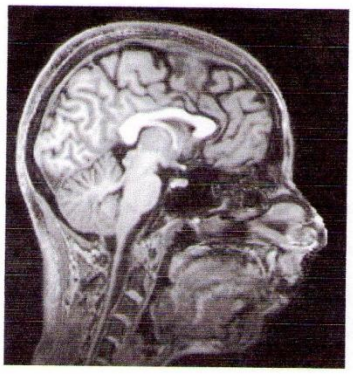
Appendix 4

THE UNIVERSITY of LIVERPOOL

MARIARC

Mersey Care NHS Trust

DEPRESSION STUDY



Research participants needed…

The University of Liverpool Division of Clinical Psychology, with Merseycare NHS Trust, are looking for people to take part in a research study. The aim is to investigate how psychological theory fits in with what goes on in our brains when we think about things while depressed. This will help to show why psychological therapies are so successful in treating depression.

We would like to recruit people who are currently depressed and *not taking any anti-depressant medication.*

Participants should also:

- Be between 18 and 65
- Be right handed
- Speak English as their first language
- Have no history of alcohol or substance misuse, brain injury, epilepsy, stroke or dementia
- Have no internal metal: pins, plates, pacemakers etc

The study involves:

- Meeting the researcher to fill in some questionnaires on your mood and personality.
- Coming along for an MRI brain scan at the University of Liverpool.
- You would receive £25 to cover your travel expenses and your time.

If you are interested in finding out more, please telephone us on:

07876 214661 or e-mail
may.sarsam@merseycare.nhs.uk

Appendix 5

Participant Information Sheet
Brain Activity and Cognitive Behaviour Therapy (CBT)

We would like to invite you to take part in a study taking place through Mersey Care NHS Trust and the Division of Clinical Psychology at the University of Liverpool. The study has been approved by the North Wales Research Ethics Committee (ref: *10/WNo3/17*). It is being carried out as part of a Doctoral award in Clinical Psychology. **You do not have to take part and your decision about whether to take part will not affect any treatment you receive.**

About the study:

People who are depressed are more likely to think about themselves in a negative way. Research suggests that this different way of thinking is linked to different patterns of brain activity. This project is trying to find out whether the brain activity of people with depression becomes more like the brain activity of people without depression after psychological intervention. This will be important for informing future psychological therapy. We would like to recruit some people who have been depressed and have had therapy.

What will it involve?

If you decide to take part we would invite you to the University of Liverpool for a Magnetic Resonance Imaging (MRI) scan. Before the scan a researcher would take some of your details and fill in questionnaires about your mood. This will take about sixty minutes. You would also be screened by an MRI nurse or radiographer who will take your blood pressure and ask some safety questions. While in the scanner, you will be asked to answer some very simple questions to investigate the activity in your brain while thinking about certain things. The scan itself will take no longer than 45 minutes, but we ask people to allow about ninety minutes for the whole process. The research will use data from your scan and previously collected data. **You are free to withdraw from the study at any point. Your information will not be used without your express permission.**

Who will have access to your information?

All your information would be kept confidential at all times, unless either the researcher identifies a significant risk of harm to yourself or other people, or something of concern is uncovered in the MRI scan. **The research team will never release any information without discussing this with you first.**

The study may be monitored by the Mersey Care Governance Committee to ensure that everything has proceeded in a satisfactory manner. If this happened your details would remain confidential.

Common questions answered

1. **Who can take part?**

Because the research involves an fMRI scan there are some exclusion criteria. You cannot be involved in the research if:

- You are under 18 or over 65 years old
- You are left handed
- You currently use drugs or abuse alcohol
- English is not your first language

2. **What is it like in the scanner?**

The MRI Scan is quite noisy but it causes no harm or long-term effects. Some people may experience slight feelings of claustrophobia in the scanner but most people find it quite relaxing. You will be able to hear and speak to the radiographers throughout the scan and you will also have a panic button to press. **If you do feel uncomfortable you will be able to notify us and we will remove you from the scanner straight away.**

3. **What if the scan shows something abnormal?**

Before the images for the research are collected we collect images to be sent to a Consultant Radiologist. The Radiologist looks at all the scans and will notify your GP if he sees anything of concern. You and your GP would then choose whether you want further investigations or treatment. If you have not heard from your GP within 5 weeks of the scan you can presume that there are no abnormal findings. The researcher, the radiologist and the University of Liverpool are not responsible for any examination or treatment that you undertake based upon these findings.

4. **What if the clinical interview shows something unexpected?**

The clinical interview will ask you simple questions about your mood and day to day life. It can highlight issues such as anxiety, depression, or drinking problems, but it would be very unusual for it to show anything that you are not already aware of. In the unlikely case that this does happen, a letter would be sent to your GP **with your permission**. The only time someone's information would NEED to be passed on is in the highly unlikely event that they expressed a significant risk of harm to themselves or other people.

5. **What's in it for me?**

We will cover your travel expenses and you will receive £20 to cover the cost of your time. We will also send you a summary about the findings of the research at the end of the study.

Thank you for your time and your interest. If you are interested in taking part please contact Debbie Watson on debbieb@liv.ac.uk or 0151 794 5530 or 0151 795 5354.

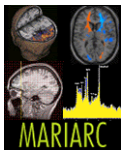
Debbie Watson, Trainee Clinical Psychologist
Division of Clinical Psychology
Whelan Building, University of Liverpool
Brownlow Hill
Liverpool L69 3GB

Appendix 6

Post-therapy Group - Demographic and Clinical Information

Participant number	Age (years)	Gender	Years of education	BDI score	Type of therapy	Number of sessions	Current diagnosis	Medication	Prev. diagnoses
1	34	f	14	3	Counselling	Unknown	None	None	PTSD
2	34	m	14	5	CBT	Unknown	None	None	PTSD
3	55	m	17	4	CBT	Unknown	None	Missing data	None
4	48	m	14	10	Unknown	Unknown	None	Missing data	None
5	21	m	17	7	CBT	12	None	Citalopram	None
6	24	f	17	10	Counselling	Unknown	None	Missing data	None
7	20	f	16	6	Counselling	6	None	Previous citalopram	None
8	21	f	17	0	CBT and counselling	20 (counselling), 16 (CBT)	None	Previous citalopram	None
9	21	m	17	2	CBT	Unknown	None	Previous fluoxetine	None
10	20	f	16	4	CBT	36	None	Prev citalopram, venlafaxine, current arapriprazole	None
11	21	f	17	5	Counselling	17	Clown phobia	None	PTSD
12	36	m	19	2	Counselling	16	None	Previous citalopram, fluoxetine	None
13	23	f	1	1	Counselling	Unknown	None	Previous citalopram	None
14	21	f	16	1	Unknown therapy and counselling	Unknown	None	Previous citalopram	None

Appendix 7



Participant Consent Form
Brain Activity and Cognitive Behaviour Therapy (CBT)

Please initial the following boxes.

I confirm that I have read the Participant Information Sheet (version 4) and discussed it with a Researcher. ☐

I have had the opportunity to ask questions about the research and my questions have been answered satisfactorily. ☐

I understand that I do not have to take part in this research. ☐

I would like to be involved in this study and I am aware that I can choose to withdraw at any point without giving a reason. ☐

Name of Researcher taking consent: _____

Signature of Researcher taking consent: _____

Date: _____

Name of Researcher Participant: _____

Signature of participant: _____

Date: _____

Thank you for your time and your interest.

Deborah Watson (Trainee Clinical Psychologist)
Division of Clinical Psychology, Whelan Building
University of Liverpool, Brownlow Hill
Liverpool L69 3GB

Appendix 8

Self>other contrast. Uncorrected for multiple comparisons. Minimum voxel size = 8 voxels. P<0.001. **Bold** text indicates areas that were also significant when the contrast was repeated using equal sized groups of participants (10) matched by age and gender.

Group contrast	Neural area		Brodmann area	Cluster size	MNI peak	T score
Control (n=12)>depressed (n=10)	**Precuneus**	**Right**	BA7	47	15 -55 49	4.81
			BA31	16	29 -76 28	3.90
			BA39	47	39 -62 34	4.11
		Right	**BA19**	19	23 -84 41	3.97
	Precentral gyrus	**Right**	**BA4**	122	32 -19 52	4.66
					25 -14 53	4.32
		Left	**BA6**	26	-41 -10 39	4.58
	Inferior frontal gyrus	**Right**	**BA45**	46	57 22 14	4.21
		Left	BA9	40	-29 22 27	3.74
					-36 29 37	3.42

	Postcentral gyrus	**Right**	**BA3**	116	40 -23 36	4.59
			BA2		55 -18 30	4.27
					63 -18 34	3.67
			BA43	58	62 -12 15	4.10
					64 -9 7	3.68
		Left	**BA40**	25	-57 -21 25	3.90
	Superior temporal gyrus	**Right**	BA30	28	47 -48 8	4.24
	Posterior cingulate cortex	**Left**	**BA31**	12	-15 -15 43	4.02
	Insula	Right	BA13	26	42 -21 4	3.88
				17	52 -6 23	3.70
Depressed (n=10)>post-therapy (n=14)	Posterior cingulate	Left	BA30	36	-6 -54 6	4.74
			BA30	12	-6 61 20	4.16
		Right	BA30	10	28 -57 15	3.93
	Precuneus	Left	BA31	19	-7 -73 30	3.99

	Thalamus	Right		12	16 -19 22	3.95
Control (n=12)>post-therapy (n=14)	Posterior cingulate	Left	BA31	59	-18 -36 30	3.94
			BA31	90	-19 -19 48	4.32
			BA24		-24 -14 45	3.82
	Insula	Right	BA13	155	37 -20 12	5.02
					29 -35 12	4.48
					40 -23 3	3.46
				75	37 19 4	4.30
					44 17 19	3.99
	Caudate	Left		10	-37 -42 8	4.24
		Right		44	20 -32 19	3.94
	Precuneus	Left	BA7	441	-14 -68 40	6.43
					-19 -60 38	5.53

		BA31		-9 -73 30	4.08
Postcentral gyrus	Right	BA2	326	40 -23 36	4.85
		BA6		51 -8 24	4.20
		BA7		61 -15 28	4.10
Inferior parietal lobule	Right	BA40	28	55 -37 42	4.01
Middle central gyrus	Left		218	-15 15 18	4.58
		BA9		-33 24 27	4.48
Precentral gyrus	Right	BA6	104	33 -9 54	4.56
		BA4		32 -19 52	4.56
	Left	BA6	41	-40 -8 39	4.35
		BA6		-39 -9 31	3.79
		BA6	54	51 4 25	4.22
				59 3 26	3.67
Midfrontal gyrus	Right	BA9	35	32 12 29	4.37

Paracentral lobule	Right	BA5	9	24 -37 52	3.84
Middle temporal gyrus	Right	BA39	177	44 -65 27	4.65
				52 -69 22	3.97
				59 -69 13	3.85
Superior occipital gyrus	Right	BA39	25	-29 -73 35	3.83
Parahippocampal gyrus	Right	BA19	10	39 -47 0	4.35
Middleoccipital gyrus	Right	BA19	28	31 -83 34	4.02
	Left	BA19	42	-40 -86 15	4.01
Lingual gyrus	Right	BA18	8	30 -79 -6	3.87
Culmen	Left		11	-10 -55 -5	3.87

Appendix 9

Self negative>other negative ANOVA (Matched groups, n=10)

(Uncorrected for multiple comparisons. Minimum voxel sixe=20 voxels. P<0.001.)

Contrast	Neural area		Brodmann area	Cluster size	MNI peak	T score
Depressed group>control group	Inferior frontal gyrus	Left	BA13	187	-37 25 3	4.90
	Middle frontal gyrus		BA46		-44 31 9	4.67
	Insula		BA13		-38 18 2	4.59
	Inferior frontal gyrus	Left	BA9	28	-53 16 19	3.73
					-45 13 19	4.36
	Precentral gyrus	Left	BA6	42	-45 8 35	4.36
Control group>post-therapy group	Precuneus	Left	BA7	32	-13 -69 46	4.53
	Posterior cingulate cortex	Right	BA31	55	18 -39 36	4.52
					14 -34 45	4.15

	Caudate tail	Left		37	-23 -29 16	4.49
	Inferior parietal lobule	Right	BA40	25	36 -43 44	4.30
	Insula	Right	BA13	51	30 -28 15	3.92
					36 -23 8	3.88

Self positive>other positive ANOVA (Matched groups, n=10)

(Uncorrected for multiple comparisons. Minimum voxel sixe = 20 voxels. P<0.001.)

Contrast	Neural area		Brodmann area	Cluster size	MNI peak	T score
Post-therapy group>control group	Anterior cingulate gyrus	Left	BA24	39	1 1 35	5.27
					1 8 20	3.52
		Right	BA24	30	16 11 28	3.85
					7 18 28	3.60
	Temporal lobe, middle temporal gyrus	Left	BA37	127	-54 -66 10	4.53

	Cerebellum, posterior lobe (declive)	Left		37	-31 -75 -14	4.34
	Insula	Left	BA13	33	-44 9 -2	4.20
	Occipital lobe, lingual gyrus	Left	BA17	31	-7 -91 8	3.93
	Cuneus	Left	BA17		-2 -100 8	3.77
Depressed group>post-therapy group	Frontal lobe, precentral gyrus	Right	BA6	81	34 11 25	5.07
					28 4 20	4.42
	Posterior cingulate	Right	BA30	93	31 -68 11	4.90
			BA31		28 -61 18	3.88
	Caudate	Left		90	-13 -25 30	4.17
Post-therapy group>depressed group	Cerebellum, posterior lobe (declive)	Left		64	-30 -81 -15	4.86

Appendix 10

Self negative-caps negative ANOVA (Matched groups, n=10)

(Uncorrected for multiple comparisons. Minimum voxel sixe = 20 voxels. P<0.001.)

Contrast	Neural area		Brodmann area	Cluster size	MNI peak	T score
Depressed group>control group	Caudate (tail)	Left		26	-15 -23 25	5.04
	Caudate (body)	Right		22	20 -16 22	4.29
	Paracentral lobule	Left	BA5	100	-9 23 25	4.81
	Dorsal anterior cingulate cortex		BA32		-13 32 34	4.38
	Superior frontal gyrus	Right	BA8	30	19 44 37	4.47
			BA6	46	20 26 49	4.09
	Inferior frontal gyrus	Left	BA13	35	-39 24 1	4.25
			BA45		-38 33 -1	4.12
	Anterior cingulate cortex	Right	BA24	160	3 24 23	4.63
	Superior frontal cortex	BA6			17 22 30	4.11

			BA24		6 33 19	3.60
		Left	BA31	44	-0 -38 35	4.55
	Posterior cingulated	Left	BA30	25	-7 -66 15	4.00
	Insula	Right	BA13	51	49 10 -11	4.45
Depressed group>post-therapy group	Caudate (tail)	Left		22	-19 -27 25	4.87
	Superior frontal gyrus	Right	BA8	27	17 44 37	4.38
			BA6	35	22 18 48	3.98
	Posterior cingulate cortex	Right	BA31	40	20 -53 20	4.51
	Anterior cingulate cortex		BA32	49	15 21 28	4.01
			BA24		5 24 23	3.87
	Precuneus	Left	BA7	27	-7 -41 53	3.96
					-16 -45 49	3.82

Self positive-caps positive ANOVA (Matched groups, n=10)

(Uncorrected for multiple comparisons. Minimum voxel sixe = 20 voxels. P<0.001.)

Contrast	Neural area		Brodmann area	Cluster size	MNI peak	T score
Depressed group>control group	Superior frontal gyrus	Right	BA6	48	23 22 50	5.21
	Superior frontal gyrus	Left	BA6	24	-8 14 61	3.95
	Medial frontal gyrus	Left	BA6		-12 16 53	3.46
	Medial frontal gyrus	Right	BA6	51	10 -2 54	3.89
	Middle frontal gyrus	Left	BA6	20	-17 3 61	4.36
	Precentral gyrus	Right	BA4	20	50 -3 50	4.06
	Anterior cingulate cortex	Left	BA32	122	-11 32 44	4.84
	Thalamus	Right		23	10 -19 4	4.28
	Superior occipial gyrus	Right	BA19	37	47 -78 34	4.01
	Cuneus	Right	BA18	20	6 -76 25	3.70

Post-therapy group>control group	Anterior cingulate cortex	Left	BA32	308	-11 30 44	6.80
	Medial frontal gyrus	BA8			-12 43 38	3.89
	Superior frontal gyrus	BA6			-11 26 55	3.56
	Anterior cingulate cortex	Right	BA24	600	7 15 33	5.15
			BA24		18 17 25	4.94
			BA24		17 10 42	4.83
			BA24	29	7 32 8	4.36
	Posterior cingulate cortex	Right	BA31	42	6 -40 32	4.06
	Claustrum	Left		200	-35 12 -2	5.68
	Precentral gyrus	Left	BA44		-43 8 2	4.96
	Putamen	Left			-22 7 11	4.39
	Postcentral gyrus	Right	BA3	108	59 -11 42	5.55
		Right	BA40	39	47 -22 46	4.07

Inferior frontal gyrus	Left	BA37	69	-45 -73 6	5.37
Middle temporal gyrus	Left	BA37		-46 -64 3	4.10
Inferior frontal gyrus	Left		41	-48 25 14	3.80
Insula	Left	BA13		-40 26 14	4.26
Inferior frontal gyrus	Right	BA20	23	66 -23 -27	4.91
		BA20		55 -32 -24	3.88
		BA8	227	35 29 37	4.46
		BA6		29 34 34	3.94
Middle frontal gyrus	Left	BA6	27	-40 9 47	4.57
Superior temporal gyrus	Right	BA22	352	56 -2 -8	5.23
Inferior fronal gyrus	Right	BA44		69 14 5	4.79
Superior temporal gyrus	BA22			61 4 -2	4.49
Anterior lobe, culmen	Right		78	14 -41 -9	4.44
Posterior cingulate	Right	BA29		13 -50 9	3.96

Precuneus	Right	BA7	35	22 -74 45	4.14
Inferior occipital gyrus	Right	BA18	23	40 -92 -11	4.20
Inferior occipital gyrus	Right	BA19	46	45 -74 -1	4.13
	Right	BA19		50 -83 -4	3.80