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Major depressive disorder is related to a broad disruption in brain regions underlying working memory processing

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Abstract of the Dissertation

Major depressive disorder is related to a broad disruption in brain regions underlying working memory processing

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Major depressive disorder (MDD) is associated with significant deficits in information processing (Clark et al., 2009). Previous studies examining the neural basis of these deficits have often focused on disruptions localized to a small number of brain regions or have used study paradigms that do not allow for an examination of component cognitive processes such as the selection and maintenance of items held in working memory (WM). Using a task previously employed to investigate selective information processing in healthy subjects (Oh & Leung, 2010), the experiment described in this thesis examined two questions regarding the effect of MDD on activity in brain regions supporting WM: (1) the specificity of disruptions related to the processing of face stimuli in extrastriate brain regions involved in selective face (and scene) processing and (2) the effect of the disorder on brain regions associated with WM selection and maintenance, including regions in the prefrontal and parietal cortices. Behavioral and brain imaging (fMRI) data were analyzed for a total of 30 (15 unmedicated subjects with MDD, 15 matched controls) subjects. Analysis of face and scene selective regions of interest revealed that MDD-related decreases in specificity were most evident in the parahippocampal gyrus and retrosplenial cortex during the functional localizer and WM selection tasks, two regions often associated with memory encoding and retrieval, rather than in regions implicated in selective face processing. Control and MDD-group subjects showed generally overlapping patterns of activity during the WM selection task. However, in analyses of overall activity during the WM task, the control group showed significant clusters in the prefrontal and parietal cortices, including the superior and middle frontal gyri and superior parietal lobe during the cue and post-cue delay phases which were not suprathreshold in the MDD group. Between-group comparisons of selection-related activity during the cue stage revealed significantly greater activity in clusters within medial occipital lobe regions, specifically the cuneus, in the MDD group subjects compared to controls. Despite these differences, group comparisons of behavioral performance were insignificant. Therefore, MDD may be associated with disruptions in brain regions associated with memory encoding, selection and retrieval, even when deficits in these processes are not immediately apparent at the behavioral level.

For my parents,

Raymond and Mary (Ty) Borghi

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List of Abbreviations

Abbreviation	Term
AMY	Amygdala
ACC	Anterior Cingulate Cortex
APFC	Anterior Prefrontal Cortex
BA	Broadmann's Area
dlPFC	Dorsolateral Prefrontal Cortex
dmPFC	Dorsomedial Prefrontal Cortex
FFA	Fusiform Face Area
IFG	Inferior Frontal Lobe
ISI	Inter Stimulus Interval
ITI	Inter Trial Interval
IPS	Intraparietal Sulcus
ITS	Intratemporal Sulcus
IDS	Inventory of Depressive Symptoms
LOT	Lateral Occipito-temportal cortex
MFG	Middle Frontal Gyrus
MOC	Middle Occipital Cortex
MOG	Middle Occipital Gyrus
NAP	Negative Affective Priming Task
NP	Negative Priming Task
OFA	Occipital Face Area
OSPAN	Operation Span Task
PHG	Parahippocampal Gyrus
PPA	Parahippocampal Place Area
PCC	Posterior Cingulate Cortex

Abbreviation	Term
RT	Reaction Time
ROI	Region of Interest
RSC	Retrosplenial Cortex
RRS	Ruminative Responses Scale
STAI	State and Trait Anxiety Inventory
sbPFC	Subgenual Prefrontal Cortex
SFS	Superior Frontal Sulcus
SPL	Superior Parietal Lobule
STS	Superior Temporal Sulcus
SMA	Supplementary Motor Area
TOS	Transverse Occipital Sulcus
vlPFC	Ventrolateral Prefrontal Cortex
VBM	Voxel Based Morphometry
WM	Working Memory

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Chapter 1
General Introduction: Neurocognitive deficits in major depressive disorder (MDD)

With a lifetime prevalence of 16 percent in the United States (Kessler et al., 2003; 2006), major depressive disorder (MDD) is extremely damaging in terms of personal and societal costs (Greenburg et al., 2003). Among the symptoms of MDD are significant disruptions in information processing (Clark et al., 2009; Thomas & Elliot, 2011) including disruptions in working memory, cognitive inhibition, and attention (Gotlib & Joormann, 2010; Hammar & Ardal, 2009). Research using brain imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have revealed disrupted activity in a broad range of brain regions in subjects with MDD compared to healthy controls (for review, Drevets et al., 2008; Koolschijn et al., 2009; Krishnan & Nestler., 2008). However, many studies designed to examine disruptions in neural activity associated with the cognitive deficits of MDD have focused on disruptions localized in two regions- the prefrontal cortex (PFC) and the amygdala.

Both the PFC and amygdala are logical targets for examining the neural basis of MDD-related cognitive deficits owing to their role in supporting processes related to emotion regulation (for review, Oschner & Gross, 2005; Phelps & LeDoux, 2005) and executive control (for review, Miller & Cohen, 2001; Sheaefer & Gray, 2007). However, three converging lines of investigation indicate that the disease arises from disruption beyond just these regions. First, work in healthy subjects has demonstrated that the cognitive processes observed to be affected during MDD, including those related to the selection and maintenance of information within working memory (Jonides et al., 2008), emerge from distributed neural networks rather than singular brain regions (see commentary by Postle, 2006). Second, the complexity and heterogeneity of MDD-related deficits in information processing point to disruption within such distributed systems, rather than being restricted to a single location (Holtzheimer & Mayberg, 2010). Third, the results of several meta-analyses of neuroimaging studies examining MDD-related cognitive deficits have demonstrated that, while aberrant activity is observed in both the PFC and the amygdala, it is not restricted to just these areas (e.g. Diener et al., 2012; Fitzgerald et al., 2006; 2008; Stuhrmann et al., 2011)

The analyses described in the following chapters were designed to examine the effect of MDD on activity in brain regions related to information processing, within and beyond the PFC and the amygdala. This introduction will provide a critical review of the growing body of behavioral and brain imaging studies examining cognitive disruption in MDD. By reviewing both the existing literature regarding cognitive disruptions in MDD and the major questions left open by research that has often focused on disruptions localized to a relatively small number of brain regions and on a small subset of cognitive processes, this introduction will lay out the significance of the experiment described in the following chapters as well as the rationale underlying its hypotheses.

The analyses described in chapter two examined the breadth and specificity of MDD-related disruptions in the extrastriate brain regions associated with the selective processing of face and scene stimuli. Examining these areas, using a task previously employed to examine selective information processing in healthy subjects (see Oh & Leung, 2010), allowed for a novel comparison of disruptions related the processing of faces compared to disruptions related to the processing of other categories of complex visual stimuli (namely, outdoor scenes). The analyses described in chapter three examined how MDD disrupts activity in brain regions, beyond those

examined in chapter two, involved in working memory selection and how individual differences in working memory (WM) task performance and MDD symptomatology relate to between-group differences in WM-related brain activity. While chapters two and three include brief discussions, chapter four provides a comprehensive overview regarding the placement of the work described in this thesis in the current body of research examining MDD from neuroscience and symptom-based perspectives.

1.1 Cognitive Deficits in MDD

Difficulties in cognition have long been examined in subjects with MDD (for review, Austin et al., 2001; Matthews & MacLeod, 2005; see also, Beck, 1967), with a recent meta-analysis demonstrating that executive control processes may be particularly affected during the disease (Snyder et al., 2012). Possibly owing to differences in subject characteristics and design parameters between studies, the results of work examining cognitive deficits in MDD using only behavioral tasks have been somewhat inconsistent (for review, Bora et al., 2012b; Hammar & Ardal, 2009; Lee et al., 2012; Rogers et al., 2005; See also, Hasselbalch et al., 2011). However, as demonstrated in the following sections, the absence of statistically significant deficits at the behavioral level does not necessarily indicate an absence of disruption at the neural level. Individuals with MDD show difficulties across multiple cognitive domains, including memory, cognitive inhibition, and attention. Though neurocognitive deficits within each of these domains have been investigated individually in subjects with MDD (for review, Clark et al., 2009; Thomas & Elliot, 2009), it is likely that disruptions in all three interact in the production of cognitive symptoms in MDD.

1.1.1 Working Memory Deficits

Because it incorporates each of the domains mentioned above, and because there is an existing literature evaluating the neural basis of WM in healthy individuals (for review, Barbas, 2000; D'Esposito et al., 2002; Jonides et al., 2008; Tanji & Hoshi, 2008), working memory (WM) is an ideal target for studying the neural basis of cognitive dysfunction in MDD. However, because studies examining MDD-related disruptions in WM have most often used designs that require subjects to use multiple WM processes simultaneously (such as the *n*-back task) or have used emotional stimuli (either positive, negative, or both), it is presently unclear how MDD relates to deficits in specific WM processes; including the updating and maintenance of information held in working memory.

Working memory is generally conceptualized as a limited-capacity system responsible for the maintenance and manipulation of information required for the completion of complex tasks (Baddeley, 1986; 2003; Baddeley & Hitch, 1974; Miyake & Shah, 1999). Because of its limited capacity, optimal WM performance requires efficient updating and maintenance of only behaviorally relevant information (Hasher & Zacks, 1988; Hasher et al., 1999; Cowan, 2010). Recent models of WM have proposed a close relationship between working memory processes and attention in the selection of relevant information (e.g. Cowan, 1988; 1999; Oberauer, 2001; 2002; 2009). Disruptions in the inhibitory and attentional processes related to WM have been specifically related to the ruminative symptoms of MDD (Joormann, 2005; Linville, 1996). In hypotheses based on this relationship, an inability to (appropriately) expel non-relevant information leads to difficulties in attending to and processing new, behaviorally relevant, information. This, in turn is hypothesized to result in rumination and the onset of depressive

episodes (Gotlib & Joormann, 2010). Empirical evidence supporting such hypotheses comes from studies demonstrating a significant negative correlation between rumination scores and behavioral indices measuring a subject's ability to overcome interference from negatively valenced stimuli (e.g. Joormann et al., 2010) and from studies indicating significant disruptions in brain regions often implicated with interference resolution, such as the anterior cingulate, inferior parietal cortex, and clusters within the dorsolateral and medial PFC (see Wager et al., 2005), in highly ruminative depressed subjects compared to controls (e.g. Berman et al., 2011; Foland-Ross et al., In Press)

A number of studies demonstrating behavioral working memory deficits in subjects with MDD have used a variant of the *n*-back task. In this task, subjects are presented with a series of stimuli and are asked to indicate if the current stimulus matches the one presented *n* steps (typically between 1 and 3) earlier in the sequence (Kirchner, 1958). Given that this task requires subjects to constantly maintain and update a number of items, it has often been used to examine the storage and processing components of working memory (Owen et al., 2005). Using a letter variant of the *n*-back task, Harvey et al. (2004) found subjects with MDD to be significantly less accurate in 1-back, 2-back, and 3-back conditions compared to healthy controls, with no significant differences observed in a baseline 0-back condition (Harvey et al., 2004). While these findings could be interpreted as evidence for a specific deficit in WM storage and/or updating (rather than an overall cognitive deficit) during MDD, a later study by Rose and Ebmeier (2006), which used a spatial version of the *n*-back demonstrated that subjects with MDD performed significantly worse than controls (both in decreased response accuracy and increased reaction time) even on the 0-back condition (Rose & Ebmeier, 2006). Though these contrasting results make it difficult to interpret the results of *n*-back studies, such findings may be due to the relative imprecision of the task rather than a lack of coherent WM deficits in MDD. Because the *n*-back task requires the simultaneous use of multiple cognitive processes- including updating, maintenance, and decision making, it is ill-suited for examining deficits in component WM processes unless paired with a battery of other cognitive tasks.

Only a few studies examining MDD-related deficits in WM have specifically examined deficits related to WM maintenance and updating. For example, Gruber et al. (2011) found subjects with MDD to be significantly impaired on verbal working memory tasks requiring articulatory rehearsal, with no significant differences observed in tasks examining the visuo-spatial component of working memory (Gruber et al., 2011). Though such results point to specific maintenance-related impairments in MDD, there is a relative paucity of research in this area. Additional research is necessary to further elucidate exactly which processes (and consequently which brain regions) are specifically affected. In one of the few studies explicitly designed to examine the possibility of deficits in working memory updating, Joormann and Gotlib (2008) found that subjects with MDD displayed increased interference from negatively, but not positively, valenced words (notably, no neutrally valenced words were included in the experimental design) compared to healthy controls (Joormann & Gotlib, 2008), with later research indicating a link between such difficulties and the ruminative symptoms of the disease (for review, Joormann et al., 2010).

Though overall working memory deficits have been observed somewhat inconsistently at the behavioral level, there is an emerging body of evidence suggesting the possibility of MDD-related deficits in component processes; including maintenance, updating, and inhibition necessary for optimal implementation of WM. To be able to examine the breadth of WM deficits, it is necessary to use experimental paradigms with two features. First, it is necessary to

use tasks that do not require the simultaneous use of multiple cognitive processes. Tasks like the *n*-back may allow researchers to examine deficits in WM overall, however it is not possible to use such tasks to examine component processes related to the maintenance and updating of information within WM. Additional research, using alternative paradigms (including delayed recognition paradigms), that require either a limited number of such processes or allow such processes to be examined at discrete points in time is therefore necessary to examine the effect of MDD on WM. Second, to fully define MDD-related deficits in WM, it is necessary to use tasks that do not employ strongly valenced stimuli. The widespread use of such stimuli has yielded robust findings concerning both behavioral and neural disruptions in information processing when subjects with MDD view positive and negative stimuli-especially human faces (Davidson et al., 2002; Stuhrmann et al., 2011; Thomas & Elliot, 2009). However, the widespread use of emotional stimuli has not allowed for a thorough examination of lower levels of information processing- including visual perception- that may be significantly disrupted during the disease (see Bubl et al., 2009). The use of non-valenced stimuli, whether they be simple visual stimuli (colors, shapes, etc.) or neutrally valenced complex stimuli (faces, scenes, objects, etc.) should, therefore, be employed in future studies examining cognitive processes that may be strongly affected during MDD.

1.1.2 Cognitive Inhibition

Contemporary theories postulate that inhibition is not a unitary construct, but rather involves several distinct components including response inhibition, cognitive inhibition, and emotional inhibition (Friedman & Miyake, 2004; Nigg et al., 2000). A growing number of studies demonstrating that subjects with MDD have significant difficulty disengaging from negative affective states (e.g. Johnstone et al., 2007; Wang, et al., 2008) indicate the presence of disruptions in emotional inhibition during the disease. In contrast, a relatively small number of studies have investigated concurrent difficulties in preventing non-relevant information (that may or may not have emotional content) from entering WM (see Gotlib & Joormann, 2010). This means that, at least compared to those related to emotional inhibition, relatively little is known about the breadth or neural basis of deficits in cognitive inhibition in individuals with MDD.

Deficits in cognitive inhibition have been shown to severely affect WM task performance- as non-relevant information may then enter, or remain held within, working memory. Such deficits have been reported in multiple psychiatric populations including children with attention deficit disorder (Alderson et al., 2007; Bjorklund & Harnishfeger, 1990), patients with obsessive-compulsive disorder (Enright & Beech, 1990; 1993), patients with schizophrenia (Frith, 1979; Westerhausen et al., 2003), and subjects with MDD (Eugène et al., 2010; Joormann et al., 2007).

The first evidence for a deficit in cognitive inhibition in MDD came from studies employing negative priming (NP) tasks. Though NP tasks differ in execution, all operate under the assumption that previously ignored material (i.e. material previously presented as a distracter) is more difficult to process if later presented as a target (Tipper, 1985; 2001). Linville (1996) was the first to investigate negative priming in MDD. She reported that depressed individuals were less likely to inhibit distracting stimuli compared to healthy controls. Specifically, while control subjects were slower to respond to letter strings that they had previously been asked to ignore, individuals with MDD failed to show this effect (Linville, 1996). MacQueen and colleagues (2000) demonstrated similar results in a study in which the color and spatial location of study stimuli were manipulated (MacQueen et al., 2000).

Though these studies, as well as studies employing large batteries of cognitive tasks (for example, Gohier et al., 2009) support the hypothesis that MDD is related to an overall deficit in cognitive inhibition, there is a growing body of literature demonstrating that such deficits may be strongest (or, at least, most behaviorally evident) in the processing of negatively valenced material. In the negative affective priming (NAP) task, reaction time is measured as subjects respond to positive and negative material that they were previously instructed to ignore (Joormann, 2004). In studies using both emotional words (Joormann, 2004) and emotional faces (Goeleven et al., 2006), individuals with MDD were shown to be significantly impaired in the inhibition of negatively, but not positively, valenced material compared to healthy controls.

Studies examining deficits in cognitive inhibition in subjects with MDD have perhaps yielded the most consistent results when negative stimuli are used. However, observations that subjects with MDD also have difficulty inhibiting neutral stimuli indicate that the disease affects cognitive inhibition in a more general way than is implied by studies showing inhibitory deficits specific to emotional stimuli. This mirrors the previously discussed findings related to working memory and findings in a domain related to both working memory and cognitive inhibition-attention.

1.1.3 Attention

As previously stated, current models of working memory posit a close relationship between attention and the selection of information held within working memory (Lepsien & Nobre, 2006; Oberauer, 2001; 2002; Oberauer & Hein, 2012). According to a review by Castaneda and colleagues (2008), deficits in attention, possibly more than any other cognitive deficit, may characterize individuals with MDD. Difficulties in attention have even been linked to the ruminative symptoms of the disease (e.g. Davis & Nolen-Hoeksema, 2000). However, a growing body of studies investigating attention-related deficits in MDD has indicated that MDD is not associated with a deficit in attention alone, but rather in the interaction between attentional and executive control processes, such as those involved in WM.

A large number of studies examining attention-related biases in MDD have used the dot probe task (MacLeod et al., 1986). In this task, subjects are presented with pairs of stimuli (words or faces), generally one emotional and one neutral. After the offset of each pair, a probe appears in the location of either the neutral or emotional stimulus. Allocation of attention is then measured by the subject's latency to detect the probe. If a subject orients selectively toward the emotional stimuli, they will be faster to detect probes that replace emotional stimuli and slower to detect probes that replace neutral stimuli (MacLeod et al., 1986). Studies using dot probe tasks with a short presentation duration (less than 1 second) have shown little difference between subjects with MDD and healthy controls (e.g. Mogg et al. 1995). However, a number of studies have documented biases when stimuli are presented for a relatively long duration (greater than 1 second) (Bradley et al., 1997; Gotlib et al., 2004). This difference indicates that MDD-related deficits in attention-related processes may occur at relatively late processing stages, a finding in line with the recent hypotheses that MDD is related not to initial orienting biases but is instead evident under conditions that require elaborative processing (Mogg & Bradley, 2005).

Dot-probe tasks have also been used to demonstrate the particular relevance of emotional faces in MDD. In two studies, Ian Gotlib and colleagues (2004; 2004b) found that subjects diagnosed with MDD showed significant orientation biases towards sad faces as opposed to happy and angry faces compared to controls (Gotlib et al., 2004; 2004b). In these studies, subjects with generalized anxiety (Gotlib et al., 2004) and social phobia (Gotlib et al., 2004b)

failed to show such biases, suggesting that this deficit may be unique to individuals with MDD. In follow-up studies, similar deficits were observed in formerly depressed adults (Joormann & Gotlib, 2007) and subjects at high risk for MDD (Joormann et al., 2007; Kujawa et al., 2010).

In a visual search task, depressed subjects did not show significantly enhanced detection of MDD-related words (for example, "depressed," "dejected," "exhaustion") when they were presented as the target, but were more distracted by the same words when they were presented as distracters (Rinck & Becker, 2005). In studies monitoring eye movements, depressed subjects have been shown to make initial saccades to negatively valenced faces (Leyman et al., 2011) and scenes (Caseras et al. 2007) equally as often as to neutral stimuli. Compared to control subjects, however, depressed subjects have been shown to fixate significantly longer on negatively valenced stimuli (Eizenman et al., 2003; Leyman et al. 2011; Caseras et al., 2007). Together these results suggest that MDD is not characterized by an automatic orientation towards negative stimuli, but rather a deficit in disengaging attention from such stimuli.

The presences of MDD-related deficits in working memory, cognitive inhibition, and attention in behavioral studies imply a complex disruption in the brain activity underlying each (see commentary by Gruber & Goscke, 2004). However, because studies examining these deficits have used paradigms that require the application of multiple processes simultaneously or used emotionally valenced stimuli (often human faces), further research is still required to delineate the precise manner in which information processing is disrupted by MDD. Behavioral studies have revealed a great deal about their character and taxonomy, but additional research is required to explicate the neural basis of information processing deficits in MDD. A recent meta-analysis of studies examining brain regions involved in the executive components of working memory has demonstrated that seemingly discrete processes involved in WM, inhibition, and attention (namely, the inhibition of irrelevant information from WM, the shifting of attention between items held within WM, and the updating of the contents WM) can be associated with activity in similar groups of brain regions within the frontal, parietal, and temporal lobes (Nee et al., 2013). While previous work examining the neural basis of MDD-related cognitive deficits has tended to focus on a limited number of regions, especially regions within the dorsolateral and ventromedial prefrontal cortex and the amygdala (see Murray et al., 2011), an investigation of how MDD affects functioning in this broader group is necessary to delineate how disruption at the neural level may underlie the heterogeneous manifestation of cognitive deficits observed in behavioral studies.

1.2 Changes in Brain Anatomy and Physiology in MDD

A comprehensive review of all MDD-related physical changes in the brain is beyond the scope of this manuscript (for concise summaries, see Belmaker & Agam, 2009; Krishnan & Nestler, 2008). Therefore, the following sections will focus primarily on changes observed in the amygdala and prefrontal cortex (PFC)- the two major regions of interest for researchers examining the neural basis of MDD-related cognitive deficits.

Both the prefrontal cortex (for review, Fuster, 2008; Stuss & Knight, 2002; Passingham, 1993) and amygdala (for review, McDonald, 1999; Pessoa et al., 2010; Sah et al., 2003) have a large number of intrinsic and extrinsic connections with both cortical and subcortical regions, making them well situated anatomically for their role in supporting cognitive behaviors such as working memory (see, Barbas, 2000) and for contributing to the symptoms of many mental

disorders including MDD (see also, Amaral & Price, 1984; Barbas & Pandya, 1989; Barbas et al., 1999; Herzog & Van Hoeson, 1976; Porino et al., 1981).

1.2.1 Morphological Changes in the Prefrontal Cortex and Amygdala in MDD

Though the neurochemistry and anatomical connections of the PFC and amygdala have recently received significant attention for their role in instantiating the symptoms of MDD, post-mortem studies have yielded significant insight into how MDD affects the cytoarchitecture of both regions (for review, Drevets et al., 2008; Rajkowska, 2003). The most widely cited finding from post-mortem studies of patients with MDD is a decrease in glial cell density in frontal and limbic regions; including the subgenual anterior cingulate cortex, hippocampus, and multiple regions within the PFC and amygdala (Bowley et al., 2002; Cotter et al., 2001; 2002; Hamidi et al., 2004; Rajkowska et al., 1999; 2001; Ongur et al., 1998). These findings are most robust in studies of younger adults, with studies using post-mortem samples of older adults demonstrating little difference in glial density between individuals with MDD and matched controls (Khundaker et al., 2009; Miguel-Hidalgo et al., 2000). The majority of post-mortem studies have not differentiated between glial sub-types, however there is growing evidence for specific losses in oligodendrocytes, at least in the prefrontal cortex (Aston et al. 2005; Uranova et al., 2001; 2004). This loss of oligodendrocytes is supported by findings of significantly less intense myelin staining in white matter from the dorsolateral and ventromedial PFC in subjects with MDD compared to healthy controls (Regenold et al., 2007; For review, Tham et al., 2011).

In addition to the relatively robust finding of prefrontal oligodendrocyte loss, MDD-related reductions in pyramidal neuron density (as measured by manual counting within slabs defined *a priori*) in the orbitofrontal PFC has been reported in some post-mortem studies (For example, Cotter et al. 2002; Rajkowska & Miguel-Hidalgo, 2005; Rajkowska et al., 1999; 2001). However these results were not replicated in later studies that indicated a decrease in pyramidal neuron size, as measured by an isotropic nucleator probe, rather than a decrease in density (e.g. Miguel-Hidalgo et al. 2005). Though the exact mechanism is still under investigation, decreased prefrontal oligodendrocyte density as well as a possible decrease in prefrontal neuron size has been postulated to be linked to elevated levels of glutamate (Dewar et al., 2003; McDonald et al. 1998) or glucocorticoids (see Banasr & Duman, 2008; Cheng & de Vellis, 2000) present during depressive episodes (for review, Drevets et al., 2008).

Beyond post-mortem studies, structural changes in the brain associated with MDD have been examined in a number of studies using voxel-based morphometry (VBM). A meta-analysis of 23 VBM studies of MDD subjects demonstrated a significant and replicable decrease in gray matter volume the rostral ACC (BA32) as well as reductions in both the dorsomedial (BA6-9) and the dorsolateral PFC (BA9) (Bora et al., 2012). The results of VBM studies specifically targeting the amygdala have been comparatively less consistent (for review, Hajeck et al., 2011; Hamilton et al., 2008), with studies showing amygdala gray matter volume in MDD-group subjects to be both significantly greater (e.g. Bremner & Narayan, 2000; Frodl et al., 2004) and significantly lesser (e.g. Caetano et al., 2004; Hastings et al., 2004; Hickie et al., 2007) than in healthy controls. This lack of a single pattern of results, however, has likely arisen from significant differences in MDD-group characteristics between studies rather than from the disease itself. A meta-analysis by Hamilton et al. (2008) demonstrates that increases in amygdala size between studies positively correlates with the proportion of subjects taking anti-depressant medication- studies that include only non-medicated subjects demonstrate a relatively robust decrease in amygdala volume (Hamilton et al., 2008)

Abnormalities in cytoarchitecture and structural volume may be related to the widely studied changes in neurochemistry during MDD. The PFC and amygdala both have direct connections to the origin of many neurotransmitter systems; including the basal forebrain (acetylcholine), the locus coeruleus (norepinephrine), the ventral tegmental area (dopamine), and the raphe nuclei (serotonin) (Krishnan & Nestler, 2008). Each of these systems has been investigated individually, and in combination, for their role in MDD (See Drevets et al., 2008; Holtzheimer & Nemeroff, 2008). MDD-related dysfunction in the neurochemistry of both the PFC and amygdala likely participates not only in the emotional symptoms of the disorder, but also contribute to attention and working memory deficits (See Price & Drevets, 2010; Manji et al., 2001).

Though promising trends are beginning to emerge from the study of other neurotransmitters, particularly glutamate (Sandi, 2011), the relationship between PFC and amygdala functioning and cognition is most established for monoamine (especially, dopamine and serotonin) systems (for review, Cools & D'Esposito, 2011; Dunlop & Nemeroff, 2007; Nutt, 2006; Seamans & Yang, 2005). Dopamine and serotonin appear to interact in modulating the firing of PFC neurons, including those involved in working memory and executive control (Di Pietro & Seamans, 2010; Luciana et al. 1998). In the PFC, dopamine exhibits an inverted-U dose response curve, where non-optimal levels (either too high or too low) impair working memory performance (Goldman-Rakic et al. 2004; Brozoski et al. 1979). Though no study has directly addressed possible interactions between MDD and dopamine-related changes in working memory, it has been hypothesized that dysfunction within the PFC-basal ganglia dopamine system may lead to a decreased level of dopamine in the PFC during MDD (See Dunlop & Nemeroff, 2007; Nutt, 2006). Similarly, a decrease in prefrontal serotonin during MDD has been implicated in the highly influential monoamine hypothesis of depression (commentary by Holtzheimer & Mayberg, 2010). Studies examining the genetic basis of MDD have pointed to a significant link between expression of the short allele of the serotonin transporter gene (5-HTTLPR) and decreased activity within the amygdala, as well as decreased functional connectivity between the amygdala and PFC in short allele carrying depressed subjects completing an emotional processing task compared to long allele carriers and healthy controls (Costafreda et al., 2013; Fu et al., 2004).

1.2.2 Metabolic and Physiological Changes in MDD

Early brain imaging studies examining MDD-related disruptions in brain activity examined resting state activity in depressed subjects compared to healthy controls. While these studies initially relied upon positron emission tomography (PET), more recent resting state studies have compared resting state activity using functional magnetic resonance imaging (fMRI). In one of the first PET studies of MDD, Baxter and colleagues (1989) found decreased glucose metabolism in the left dorsal anterolateral PFC in subjects with MDD and bipolar disorder compared to subjects with obsessive-compulsive disorder (with and without concurrent depression) and healthy controls (Baxter et al., 1989). Demonstrating a more complicated pattern of glucose activity in the PFC, Biver and colleagues (1994) later found a pattern of increased glucose metabolism in the orbitofrontal PFC and decreased metabolism in the dorsolateral PFC and parietal cortices (Biver et al., 1994). This pattern has since been replicated in multiple PET studies (See Drevets et al., 2002), with some studies demonstrating a degree of reversibility in these abnormalities following successful treatment with antidepressants (Bonne et al., 1996; Rubin et al., 1994).

Because of technical challenges (see Drevets et al., 2002), a relatively small number of studies have examined MDD-related disruptions in amygdala metabolism. An early study by Drevets et al. (1992) indicated significantly greater glucose metabolism in the left amygdala in MDD subjects compared to controls- a finding that has since been replicated in aged subjects with MDD (Mentis et al., 1995), bipolar patients in a depressed state (Ketter et al., 2001), subjects experiencing their first depressive episode (Nofzinger et al., 1999), and in MDD subjects using significantly more precise PET imaging and analysis techniques (Drevets et al., 2002). However, owing to the technical difficulty in imaging the amygdala PET studies have demonstrated inconsistent differences between MDD subjects and controls in regards to amygdala metabolism (Abercrombie et al., 1996; 1998).

Together, findings of disrupted metabolism in both the prefrontal cortex and amygdala have informed the highly influential model of MDD proposed by Helen Mayberg and colleagues. In this model, MDD is thought to arise from dysregulation in the functional connections between a number of limbic and cortical brain regions (Mayberg, 1997; Mayberg et al.,1999; Seminowicz et al., 2004). Remission, then, is thought to occur when the regulation of these connections is re-established; a hypothesis that has been supported empirically by studies examining recovery from depression following antidepressant treatment (Mayberg et al., 2000) and deep brain stimulation in otherwise treatment resistant patients (Mayberg et al., 2005; Holtzheimer et al., 2012). Because this model asserts that MDD arises from disruptions between a number of region implicated in cognitive, emotional, and autonomic functions, it stands that symptoms in each of these domains may arise from disruptions in different locations (Holtzheimer and Mayberg, 2011), which, in turn, could be modulated with different forms of treatment (Katz et al., 2010). Thus, though the results of the analyses discussed in the following chapters may not address aspects of the mood or phenomenological symptoms of MDD, they do contribute to our understanding of how the disease affects neural systems associated with cognitive processing.

1.2.3 Functional Deficits in MDD

Chapters two and three of this thesis each contain critical summaries of functional brain imaging research relevant to their respective hypotheses. For this reason, this section will provide only a brief, and relatively general, overview of the aberrant patterns of brain activity observed in MDD-group subjects. Several meta-analyses of neuroimaging studies of MDD have indicated significant MDD-related disruptions in both PFC and amygdala activity when depressed subjects complete tasks requiring information processing; including n-back tasks, Stroop tasks, associative learning tasks, and tasks requiring the processing of face stimuli (Diener et al., 2012; Haldene & Frangou, 2006; Fitzgerald et al., 2006; 2008; Stuhrmann et al., 2011). However the direction, laterality, and scale of these disruptions vary a great deal between studies and task paradigms. Adding to the complexity of these results, a relatively large number of studies have investigated neural activity associated with executive control and working memory processes using emotional stimuli. Such studies have demonstrated aberrant activity in a wide variety of brain regions including both the amygdala and prefrontal cortex (for review, Murray et al., 2011; Drevets, 2008). By comparison, there are a relatively small number of studies investigating MDD-related cognitive deficits using stimuli lacking explicit emotional content. Despite their small number, these studies indicate that disrupted activity- present in networks of brain regions that include, but are not limited to, the prefrontal cortex and amygdala- underlie the deficits in working memory, cognitive inhibition, and attention observed in

behavioral studies. Furthermore, these studies imply that such deficits are present even in the absence of a valenced stimulus.

A number of functional imaging studies have directly compared task-related brain activity in depressed subjects to those in healthy controls. Using similar paradigms as the behavioral studies (n-back tasks, delayed recognition tasks, etc.) alongside functional neuroimaging, these studies have directly examined the relationship between cognition, brain activity, and MDD. The results of these studies have been quite varied; with some studies demonstrating significantly increased levels of activation in MDD group subjects compared to controls, while others show significantly decreased levels of activation. Though such varied results are still often observed (see Thomas & Elliot, 2009), such differences are now commonly ascribed to differences in task performance between subject groups (Rogers et al., 2005). In studies where depressed subjects achieve a similar level of performance as controls on WM-related tasks (For example, Harvey et al., 2005; Fitzgerald et al., 2008), PFC hyperactivity is often observed in the MDD group subjects. In contrast, MDD-related performance deficits on WM tasks are often observed alongside PFC hypactivity (For example, Elliot et al., 1997). This trend has led to the hypothesis that the hyperactivity observed in high performing subjects represents compensatory activity- such as additional recruitment of PFC neurons- that compensates for the general decrease in PFC activity observed in resting-state studies (Walter et al., 2007). Though this claim has not yet been examined systematically in a group of high and low performing MDD subjects, similar patterns and similar interpretations have been made in studies including subjects with schizophrenia (Minzenberg et al., 2009) and elderly subjects (Reuter-Lorenz & Cappell, 2008).

1.3 The Present Study: Analyses and Hypotheses

The analyses described in the remainder of this thesis were designed to contribute to the growing body of studies examining how major depressive disorder affects brain activity related to the selective processing of information. The analyses described in chapter two were designed to investigate the specificity of MDD-related deficits in the selective processing of face stimuli. Building upon these analyses, those described in chapter three were designed to examine the effect of the disease on the congregation of brain regions that support the selection and maintenance of information in working memory.

Current hypotheses support category specific activations in visual association regions, with regions in the fusiform and parahippocampal gyri showing greater activation in response to faces (e.g. Kanwisher et al., 1997) and scenes (e.g. Epstein & Kanwisher, 1998) respectively. In addition to these regions, the selective processing of faces and scenes involves functionally and anatomically separable networks that include regions in the temporal and occipital lobes and subcortical regions such as the amygdala (for review, Haxby et al., 2010; Nasr et al., 2011). Based on the body of behavioral and imaging studies indicating that MDD-related difficulties in information processing may be especially severe in tasks requiring the processing of faces (for review, Stuhrmann et al., 2011), we predicted that subjects with MDD would show significant and specific disruptions in the face processing network compared to healthy controls in a task requiring the selective processing of both faces and scenes (see Figure 1.01). Because regions in the scene-processing network, especially the parahippocampal gyrus and retrosplenial cortex, have been implicated in memory encoding and retrieval (e.g. Aminoff et al., In Press; Burgess et al., 2001; Cabeza et al., 2004) and because several studies have pointed towards a general deficit

in visual perception in MDD (e.g. Bubl et al., 2010; 2012; Desseilles et al., 2009; 2011), we alternatively predicted that MDD could be associated with a disruption in both the face and the scene processing networks.

Current hypotheses regarding the neural basis of WM hold that the processes involved in controlling the contents of WM emerge from activity in a broad network of brain regions that include, frontal and parietal (Leung et al., 2004; Linden et al., 2003; Todd & Marois, 2004) and and subortical areas (e.g. Robinson et al., 2012). However, brain imaging have often focused primarily on the dorsolateral and ventromedial PFC due to their involvement in "executive" (Miller & Cohen, 2001) and "emotional" (Oschner & Gross, 2005) processes respectively. Because of the emergent properties of WM (see Postle, 2006), we hypothesized that subjects with MDD would show significantly disrupted activity within the WM-associated regions beyond the dlPFC and vmPFC. Because of a previous line of research demonstrated hypoactivity in WM-related brain regions (including the vlPFC, basal ganglia, and regions in the parietal cortex) in MDD subjects completing a selective information processing task (e.g. Walter et al., 2007; 2007b; Vasic et al., 2009), we predicted that the subjects in the present study would show a similar disruption. However, because a number of previous studies investigating MDD-related neurocognitive deficits have demonstrated a pattern of hyperactivity in MDD-group subjects performing at the same level as healthy controls (see Rogers et al., 2006), we alternatively predicted that we could observe performance-related hyperactivity in brain regions associated with working memory.

Chapter 2

Activity in extrastriate brain regions associated with the selective processing of faces and scenes is significantly disrupted in major depressive disorder

2.1 Chapter Introduction

Due to their strong social and emotional content, human faces may be the most commonly used stimuli for studies investigating information processing deficits in MDD (Stuhrmann et al., 2011). Because previous research has focused on regions of interest including clusters within the dorsal and ventrolateral prefrontal cortex, orbitofrontal cortex, and amygdala (for review, Gotlib & Hamilton, 2009), it remains unclear how MDD affects processing in ventral occipital and temporal brain regions associated with the perception of faces. Furthermore, since previous studies have primarily examined the emotional aspects of faces, it is presently unclear whether or not basic face-processing is intact during the disease.

In behavioral experiments, subjects with MDD often show disruptions in face-processing across a spectrum of cognitive domains including enhanced memory for negative (but not positive or, in some cases, neutral) faces (Hamilton & Gotlib, 2008; Ridout et al., 2003), increased attention towards negative faces (Gotlib et al., 2004a; 2004b), and, perhaps most consistently, in deficits in the recognition of facial expressions (e.g. Bistricky et al., 2011; Gollan et al., 2010; Leppänen et al., 2004). Studies in which subjects are asked to judge the emotional content of a face (e.g. happy vs. sad), often report that depressed subjects show a significant negativity bias compared to controls (e.g. Joormann & Gotlib, 2010). However, when subjects with MDD are asked to rate or categorize emotionally neutral stimuli, biases in both the negative and positive direction have been observed (Gollen et al., 2008; Gur et al., 1992; Leppanon et al., 2004). This indicates that the mood congruency hypothesis (Bower et al., 1981) is, on its own, insufficient to explain face-processing deficits in MDD.

Because basic visual processing deficits have been observed in subjects with MDD at both the behavioral (Bubl et al., 2010; 2012; Golomb et al., 2009) and neural (Desseilles et al., 2009; 2011) level, it is possible that MDD-related disruptions in the processing of face stimuli may reflect a more fundamental deficit in visual information processing. Subjects with MDD have demonstrated both altered perception of spatial contrast gratings (Golomb et al., 2009) and decreased contrast gain in the retina (Bubl et al., 2010; 2011) compared to healthy controls. At the neural level, subjects with MDD have shown both decreased activity in the visual cortices (specifically, V4) (Desseilles et al., 2009) and decreased functional connectivity between the visual and parietal cortices (Desseilles et al., 2011) during a visual information processing task. Due to the presence of such potentially basic visual processing deficits in MDD, it is necessary to directly examine the processing of faces relative to the processing of other, non-face, stimuli in the absence of an emotional context.

Studies examining healthy subjects indicate that the processing of faces involves a distributed network of brain regions that includes both "core" and "extended" aspects (Kanwisher et al., 2006; Haxby et al., 2010). Regions in the core network for face processing include the fusiform (FFA) and occipital (OFA) face areas as well as the superior temporal sulcus (STS) (Hoffman & Haxby, 2000; Gauthier et al., 2000; Kanwisher et al., 1997). While the FFA, OFA, and STS are believed to be involved primarily in processing the visual characteristics of faces, an extended network, including the amygdala, insula, temporoparietal junction, and medial prefrontal cortex (for review Haxby et al., 2000; Ishai, 2008; Ishai et al., 2005) is hypothesized to

be involved in processing their social and emotional content. Recent evidence demonstrating that the FFA and OFA play causal roles in face processing comes from studies demonstrating that electrical stimulation of these regions leads to significant deficits in face categorization (Chong et al., 2013) and face naming (Jonas et al., 2012). Similarly, a causal role for the STS in the perception of biological motion (such as motion necessary for the projection of emotion through facial expressions) has been established by experiments using rTMS (Grossman et al., 2005; Pourtois et al., 2004). Significant anatomical and functional connections between regions in the face processing network have been found in both humans (Fairhall et al., 2007; Furl et al., 2013; Gschwind et al., 2011; Herrington et al., 2007; Sabatinelli et al., 2005; Vuilleumier et al., 2005) and non-human primates (Freese & Amaral, 2008), which underlines the necessity of examining MDD-related disruptions in face processing in this group of brain regions rather than focusing on individual regions such as the amygdala.

Though we can find no previous studies that have directly examined disruptions in regions in the core face-processing network during MDD, convergent evidence for such a disruption comes from several sources. First, MDD-related disruptions in the fusiform gyrus have been reported in multiple studies principally examining activity related to viewing positive and negatively valenced faces in the amygdala (e.g. Fu et al., 2008; Surguladze et al., 2005; Suslow et al., 2010) and in meta-analyses examining disrupted neural activity related to emotional and cognitive difficulties in MDD (Diener et al., 2012). Notably, Surguladze et al. (2005) found that subjects with MDD showed linear increases in the activity of both the right fusiform and bilateral parahippocampal gyri in response to expressions of increasing sadness while healthy controls did not. Second, work with other psychiatric populations, including individuals with autism spectrum disorder (ASD) (Dalton et al., 2005; Kleinhans et al., 2008), schizophrenia (Walther et al., 2009) as well as aged populations (Goh et al., 2010; Park et al., 2004), have all demonstrated disrupted activity in visual association cortices. Of particular relevance to the present study, aged subjects have been shown to exhibit both behavioral WM deficits and significantly decreased selectivity, as measured by a dedifferentiation of category specific activity in ventral visual cortices including the fusiform gyri, compared to younger subjects (Park et al., 2004).

The scene processing network, which is functionally and anatomically distinct from the face processing network (Epstein & Kanwisher, 1998; Nasr et al., 2011), and includes the parahippocampal place area (PPA), transverse occipital sulcus (TOS), and retrosplenial cortex (RSC), presents an ideal target for examining the uniqueness of face processing deficits in MDD. Within this network, the PPA is hypothesized to be involved in processing the visual-spatial structure of a scene (Epstein & Kanwisher, 1998) while the RSC is hypothesized to process information related to spatial navigation (Epstein et al., 1999; 2003; Park & Chun, 2009). At present, the precise role of the TOS in this network remains unclear. In addition to their role in the selective processing of visual stimuli, both the face and scene networks have been studied for their role in working memory (WM) (e.g. Lepsien & Nobre, 2007), with previous research from our laboratory demonstrating that the PPA appears to be involved in the selective maintenance of scene (over face) stimuli (Oh & Leung, 2010).

In parallel to work investigating their involvement in the selective processing of scenes, a line of research has investigated the parahippocampal gyrus and retrosplenial cortex for their involvement in the retrieval of both spatial and non-spatial memories (Burgess et al., 2001; Cabeza et al., 2004) and in the establishment of contextual associations (Aminoff et al., 2008; Bar et al., 2008; Epstein et al., 2007; Ranganath, 2010). Thus, examining (potential) processing

disruptions in the face and scene networks allows us to not only examine the neural basis of MDD-related deficits in face processing (or possibly in visual processing in general), but also also grants us a degree of insight into how MDD-related processing deficits may relate to activity in the wider network of brain regions associated with information processing.

Based on the existing literature, the branch of analysis described in this chapter proceeded with two central hypotheses. In line with previous research, we predicted that brain activity during the selective processing of faces would be significantly disrupted in subjects with MDD compared to healthy controls (see Figure 1.02). To evaluate the specificity of face-related disruptions, we used a region of interest (ROI) approach to examine activity in regions within the core face and scene processing networks during different phases of a working memory task involving the selective maintenance of emotionally neutral faces and scenes. Second, given the involvement of regions within the face and scene networks in working memory processing, we predicted that disruptions in these regions would relate to measures of working memory performance and MDD symptomatology. To test this, we calculated a selectivity index value, examining the degree to which a region showed selective activity towards a preferred visual category (face versus scene), for each ROI. We then examined correlations between these indices and measurements of response accuracy and reaction time for the working memory task as well as scores on questionnaires measuring MDD symptoms.

2.2 Methods

2.2.1 Participants

Study participants included 19 currently unmedicated individuals with MDD and 17 healthy controls. Because of excessive motion, 4 subjects with MDD and 2 healthy control subjects were excluded from the fMRI analyses, leaving 15 matched subjects in each group. Not included in the above totals, are three subjects recruited to be in the MDD-group who did not complete the experiment due to experiencing a high level of anxiety while inside the MRI scanner.

All MDD group subjects met DSM-IV criteria for major depressive disorder as measured by the Structured Clinical Interview for the DSM-IV (SCID) (First et al., 1997). Exclusion criteria for the MDD group included the presence of any significant axis I disorder other than MDD, use of antidepressant medication, and any significant health problems. On average, MDD-group subjects had a relatively low number of past depressive episodes (range: 1-12, average: 3.01, standard deviation: 3.17), however the duration of such episodes ranged from several weeks to several years. For MDD group subjects, the SCID typically lasted between 0.5 and 1.5 hours.

Healthy control group subjects were also screened using the SCID. Exclusion criteria for control group subjects included the presence of any DSM disorders or any other significant health concerns. For control group subjects, the SCID typically lasted less than 0.5 hours. MDD and control group subjects were matched in terms of gender, ethnicity, age, and education (see Table 2.01).

2.2.2 Experimental Stimuli

A total of 320 visual stimuli were used in this experiment. The WM selection task used 90 novel face (50% male, 50% female) and 90 novel scene stimuli (50% houses, 50% city), while the functional localizer task used an additional 20 face, 20 scene, and 20 object images. An

additional 30 unique face and scene images were also added to the post-memory and valence rating tasks as "new" stimuli.

Face and scene images were drawn from several pre-existing databases and modified for the purpose of this study. Face images were drawn from the Korolinska face database (Lundgvist et al., 1998) and those created by The Center for Vital Longevity (Minear & Park, 2004). To reduce low-level visual differences between face stimuli, face images included only male and female Caucasians (50%, 50%) between the ages of 20 and 30. All faces were cropped to remove obviously differentiating features such as hairstyle, clothing, and jewelry. Scene images were drawn from the LabelMe database (Russell et al., 2008). Scene images depicted urban buildings (50%) and houses (50%) and were cropped to remove obviously differentiating features including visible text, human figures, and motor vehicles. Object images, including images of articles of clothing (shirts, hats) and kitchen equipment (bowls, cups), were taken from the Hermera Photo Objects collection (Gatineau, Quebec, Canada).

2.2.3 Face/Scene Localizer

Regions of interest within face and scene networks were defined individually for each subject. As in previous studies examining these areas (e.g. Fox et al., 2009; Oh & Leung, 2010; Xu et al., 2013), regions of interest were defined for each subject using peak coordinates extracted from a functional localizer task. The localizer task consisted of a 1-back task, featuring 12 counterbalanced blocks of face (four blocks), scene (four blocks), and object (four blocks) stimuli. Within each block, stimuli were presented for 800ms with a 1200ms ISI. Each block was 16s in duration and was preceded and followed by 16s of fixation. A diagrammatic representation of the localizer task is shown in figure 2.01a.

For three subjects (all in the healthy control group), the functional localizer contained only face (four blocks) and scene (four blocks) stimuli. After data was collected from these subjects, the localizer was updated to include object stimuli in order to facilitate a future study, not included in this manuscript, involving multi-variate pattern analysis. Because none of the comparisons discussed in this thesis involved the object blocks, all three of these subjects were included in the group level analyses described in this and the following chapter.

2.2.4 The WM Selection Task

A delayed recognition task previously used by our laboratory to study WM selection in regions within the face and scene processing networks (Oh & Leung, 2010) was adapted for use in the present study. Each run of the WM selection task included selection and non-selection trials (see Figure 2.01b). In selection trials, following 4000ms of fixation (including a 200ms warning), subjects were shown a sequence of one face and one scene image, each presented for 800ms with a 200ms ISI. After presentation of the second image, a checkerboard mask was shown for 800ms. Following a 2200ms delay period, subjects were cued to selectively remember either just the face (cue: Face) or just the scene (cue: Scene) during the subsequent 9000ms delay period. Following this delay, subjects were asked to respond whether or not a probe image (1000ms) matched the cued image (50% match/50% non-match). All cues were 100% informative.

Non-selection trials proceeded similarly, but with a cue instructing subjects to remember both the face and scene images (cue: Both) during the delay period. In non-selection trials, subjects responded whether or not the probe item was among the two items presented earlier in the trial (50% match/50% non-match). Probe items consisted of face and scene images equally.

Each trial was followed by a variable ITI (8000ms, 10000ms, or 12000ms), making the average total trial duration 30s. Subjects completed six runs consisting of 12 trials while in the scanner, each with four select-face trials, four select-scene trials, and four non-selection trials. Match and non-match trials were distributed equally within blocks. Except in match trials, where the cued image was shown twice (once during the initial presentation phase then again during the probe phase), no face or scene image was repeated during the WM selection task.

Presentation order for selection and non-selection trials was counterbalanced between runs. Within each run, positive and negative responses were balanced for each cue condition. Similarly, the presentation order of face and scene stimuli was counterbalanced for each cue condition. Stimuli-type (male vs. female, building vs. house) was counterbalanced between trials of the same type and trials in the same run. Trial orders for each run were constructed such that no more than three responses of the same type (positive vs. negative) were presented consecutively.

Response accuracy and reaction times were recorded for each trial. Reaction times were ultimately calculated for correct trials only. The behavioral benefit of selection for, both face and scene stimuli, was calculated for each subject by subtracting the average reaction time (RT) from selection trials from the average RT of the non-selection trials for each stimuli category.

2.2.5 General Experimental Procedure

All subjects were scanned less than one week following the completion of their SCID. Immediately before scanning, subjects completed a battery of questionnaires including the inventory of depressive symptomatology (IDS) (Rush et al., 1996), the ruminative responses scale (RRS) (Nolen-Hoesksema & Morrow, 1993), and the state questionnaire from the trait anxiety inventory (STAI) (Speilberger et al., 1983).

Subjects were trained on the functional localizer and WM selection task prior to scanning. Practice runs included task parameters similar to those completed in the magnet, but featured unique face, scene, and object stimuli. For the localizer task, subjects completed practice runs that included three blocks (1 face, 1 scene, 1 object). If, at the end of this training subjects were still unsure about the procedure for this task, they completed another practice run. No subject required more than two practice runs for the functional localizer. For the WM task, subjects completed practice runs that were identical to those they were to complete in the magnet. Subjects completed sufficient practice runs to achieve greater than eighty percent response accuracy. No subject required to more than three practice runs of the WM task.

To prevent subject distress and minimize motion-related artifacts during scanning, subjects were acclimated to the MRI scanning environment for 10-15 minutes using the mock-MRI scanner located in the Psychology department at Stony Brook University. Including the completion of questionnaires, training, and mock scanning, the completion of all pre-scanning tasks required approximately one hour.

While in the magnet, subjects made responses by pressing a button on a button box using their index finger. Visual stimuli were presented using E-Prime 2 (Psychology Software Tools, Pittsburgh PA). All face, scene, and object images were cropped to 186 x 250 pixels, gray-scaled, and equalized for brightness. The background of all images was filled with a uniform gray (RGB: 139, -137, -137), as was the background display during the WM selection task and all post-scanning behavioral tasks. Including the collection of both anatomical and functional images, subjects were in the magnet for approximately one hour.

Following scanning, subjects completed an additional series of behavioral tasks. To examine memory strength for cued and non-cued images, subjects were asked to complete a post-memory task. In this task, subjects were asked to identify if face and scene images were or were not presented during the preceding WM task. All face and scene images from the WM task were presented during this task, as were 60 new (not previously seen) images.

Though all images in the present study were judged to be emotionally neutral, all subjects were also asked to rate the valence (-5 = very negative, 5 = very positive, 0 = neutral) of each stimuli presented during the prior phases of the experiment. This was done to disentangle the potential confound of MDD group and healthy control subjects attributing different emotional content to face and scene images.

Finally, after completing the post-memory and valence rating tasks, all subjects completed an automated version of the operation span task (Unsworth et al., 2005). After completion of these tasks, subjects were asked to complete another state questionnaire from the STAI, the trait questionnaire from the STAI, and were debriefed (see table 1.01).

All subjects were paid for their participation. The completion of all post-scanning tasks required approximately one hour, meaning that subjects spent a total of approximately three hours in the lab on the day of scanning. Depending on the duration of their SCID, this meant that subjects spent a total of between 3.5 and 4.5 hours participating in this experiment. Subjects were paid for their participation.

2.2.6 Image Acquisition Parameters

Whole-brain images were acquired using the Siemens Trio 3T system (Siemens, Erlangen, Germany) located at Stony Brook University. High-resolution anatomical images were acquired with both a T1-weighted gradient echo pulse (MP RAGE) sequence (TR = 1900ms, TE = 2.53ms, flip angle = 9 degrees, Matrix = 256 x 256, FOV = 250 x 250mm, 176 slices, voxels = 0.98 x 0.98 x 2mm) and a T1 in-plane anatomical volume (TR = 300, TE =5, flip angle = 60 degrees, Matrix = 256 x 256, FOV 220 x 220mm, voxels = 0.86 x 0.86 x 4.03mm), consisting of 33 axial (3.5mm with a 0.5mm gap, collected ascendingly and sequentially) slices collected parallel to the anterior-commissure posterior commissure (AC-PC) line.

For functional scans, volumes were acquired using a T2* weighted EPI sequence (TR = 2000ms, TE = 30ms, flip angle = 80 degrees, Matrix = 72 x 72, FOV = 220 x 220mm, voxel size = 3.1 x 3.1 x 3.5mm, 180 volumes collected per run of the WM task, 200 volumes for the localizer). Each functional volume consisted of 33 axial slices (3.5mm with a 0.5mm gap, collected ascendingly and sequentially). Three additional (dummy) volumes were acquired at the beginning of each functional run to allow the MR signal to reach equilibrium. These volumes were discarded from the dataset before image processing and analysis.

A total of 7 functional runs were collected for each subject (including the localizer). Because of supra-threshold motion (greater than 0.5mm within a functional run, greater than 5.0mm over the course of the whole experiment) as detected manually and via the ArtRepair toolbox (Mazaika et al., 2005), approximately 8.08% of runs were removed overall. The two groups had an identical range of number of runs removed (0-2).

2.2.7 Image Processing Parameters

Preprocessing and statistical analyses were conducted using SPM8 (Wellcome Department of Cognitive Neuroscience, London, UK; www.fil.ion.ucl.ac.uk/spm). Functional images were corrected for differences in slice timing. Head motion was corrected using a six-

parameter rigid-body correction to re-align each image to the first volume of the middle run. Runs with greater than 3mm in translational or 1.5 degrees in rotational motion were removed from later analyses. High-resolution images were segmented into gray and white matter and co-registered with the mean functional image. Images were normalized to the MNI gray matter template using a 12 parameter affine registration followed by nonlinear transformations. Functional images were then smoothed with a 6mm FWHM Gaussian kernel.

Image distortion and spin history errors caused by scanner spikes were repaired by interpolation from the nearest unaffected volumes using the ArtRepair toolbox (Mazaika et al., 2005; http://cibsr.stanford.edu/tools/ArtRepair/ArtRepair.htm), an SPM toolbox commonly used to recover datasets with motion artifacts in studies examining psychiatric populations (Mazaika et al., 2005; 2007; 2009). Runs with 10% or more repaired volumes were excluded from all subsequent analyses. An independent samples t-test comparing number of repaired volumes between groups was insignificant [$t(28) = 1.21$, $p=0.24$], though on average more volumes were repaired in the MDD group (range: 7- 76, mean = 35.1) than the control group (range: 7- 52, mean = 23.5).

2.2.8 SPM Analyses

The General Linear Model (GLM) was used to construct a design matrix for the functional localizer for each subject. Epochs for each block category (face, scene, object) were modeled with a boxcar function and convolved with a canonical hemodynamic response function.

For the WM selection task, onset times for the presentation of the stimuli, the cue, the middle of the post-cue delay period, and the probe were defined for each cue condition. The onset times and duration of these event within any given trial were as follows: stimuli (onset = 4s, duration = 2s), cue (onset = 9s, duration 1s), delay period (onset = 14.5s, duration 0s), and probe (onset = 19s, duration = 2). Following a procedure used in previous studies of delay-related activity (e.g. Postle et al., 2000), the middle of the delay period (5.5 seconds after the onset of the cue) was used as an onset vector for the delay period.

Individual contrast images from the functional localizer and working memory tasks were included in second-level group analyses designed to examine different patterns of activity between the MDD and control groups. For within-group contrasts, a one-sample t-test was applied to assess effects of interest using the corresponding contrast images from each subject within each group. Between group contrasts were constructed similarly, but with contrast images entered into an independent means t-test. Clusters were first examined at a pre-specified threshold ($p < 0.001$, voxel extent: 6). Clusters observed at this threshold were considered statistically significant only if they survived FDR correction at the cluster level (Chumbly & Friston, 2008; Friston et al., 1991; 1995; Genovese et al., 2002).

2.2.9 Region of Interest Definition

Region of interest (ROI) analysis was conducted using the MarsBar toolbox for SPM (Brett et al., 2002; http://marsbar.courceforge.net). ROIs in the face network included the (bilateral) FFA, OFA, STS, and amygdala. ROIs in the scene-processing network included the (bilateral) PPA, RSC, and TOS. To define face and scene selective ROIs, face>scene and scene>face contrasts from the functional localizer task were examined at a relatively low threshold for each subject ($p < 0.001$, uncorrected; 0.01 uncorrected if no significant clusters were visible at higher threshold). If significant clusters were not visible at these thresholds,

face>baseline and scene>baseline contrasts were examined using a similar procedure (at the $p < 0.001$ threshold only). Coordinates for peak clusters within individual contrasts were then compared to mean coordinates from previous studies (e.g. Oh & Leung, 2010). Spherical 5mm ROIs were constructed at peak coordinates within 10mm of the group mean. When there were no visible clusters for a particular ROI or when visible clusters were greater than 2.5 standard deviations away from either the group mean or coordinates reported in previous studies, average coordinates were used.

Group contrasts showing face and scene network ROIs for the healthy control and MDD groups are shown in figure 2.02. Average coordinates for each ROI are shown in table 2.07. In general, average coordinates did not significantly differ between MDD and control group subjects. However, clusters (and therefore ROIs) were significantly more ventral in the left [$t(26)=3.14$, $p<0.01$] and right [$t(27)=2.05$, $p<0.05$] PPA for MDD group subjects compared to controls.

2.2.10 Selectivity Index Calculation

A selectivity index, representing the degree to which a region selectively responded to face or scene stimuli, was calculated for each ROI. To calculate this value, face and scene-related activity was extracted from each ROI for each subject during the functional localizer task and the cue, delay, and probe phases of the working memory task. As in previous studies examining selectivity in face network regions (i.e. Grill-Spector et al., 2006), a selectivity index values was computed using the following formula:

$$Selectivity = \frac{Nonpreferred - Preferred}{Nonpreferred + Preferred}$$

To calculate selectivity in face network ROIs during the functional localizer task, average percent signal change during face blocks was entered as the preferred value and average signal change during scene blocks was entered as the non-preferred value. The reverse procedure was used to calculate selectivity for scene network regions. To calculate selectivity during the WM task, complementary procedures were used for face and scene selection trials during the cue, delay, and probe phases.

To prevent inflation of selectivity indices due to the inclusion of negative signal change values, we instituted the following procedure: First, regions of interest with negative percent signal change values at any time point of either the functional localizer (see figures 2.03) or the WM task (see figure 2.05) were identified for each subject. Then, for each identified region, a constant equal to the additive inverse of the most negative time point was added to all signal change values for that region- thus raising the lowest value to zero while maintaining the distance between the signal change curves for the preferred and non-preferred stimuli (for reference, see figure 2.07b).

This correction was especially important when calculating selectivity in ROIs that exhibited negative signal change for all conditions after baseline (i.e. the left and right RSC). This procedure has been used in previous studies investigating selectivity within the face and scene networks (i.e. Simmons et al., 2007).

2.3 Results

Healthy control and MDD group subjects did not significantly differ in measures of task performance (overall response accuracy, RT, and selection benefit), working memory capacity (as measured by the operation span), or the degree to which face and scene network ROIs could be identified from the localizer task results. Control and MDD group subjects demonstrated no significant differences in regional specificity during the localizer task. Similarly, while decreased specificity for the appropriate visual category was detected in face and scene network ROIs among MDD group subjects during the post-cue delay period of the WM task, between-group comparisons did not reach significance with two-tailed tests and were insignificant. When regional specificity for the preferred visual category (faces or scenes) was quantified for each ROI in each subject individually, MDD-related decreases in selectivity approached, but did not reach, statistical significance. However, significant correlations emerged between selectivity index values for both face and scene network ROIs and measures of task performance and disease severity. Such correlations were significant only in MDD group subjects.

2.3.1 Behavioral Results

Aside from measures of MDD symptomatology, the healthy control and MDD groups scored quite similarly across all behavioral measures. These results are summarized in table 2.01. Response accuracy and reaction time data was analyzed by independent samples t-test. Group differences in overall response accuracy and reaction time for the WM task where insignificant [accuracy: $t(28) = 1.61$, $p = 0.12$; RT: $t(28) < 1$], though the healthy control group showed slightly higher response accuracy (mean: 88.22%, stdev: 7.61%) than the MDD group (mean: 83.81%, stdev: 7.34%) and MDD-group subjects were slightly faster (mean: 1044.87ms, stdev: 249.58ms) than controls (mean: 1080.15, stdev: 251.37ms). When examined using a one-way analysis of variance (ANOVA), a main effect of probe type on response accuracy was significant [$f(1,28) = 5.86$, $p < 0.05$], with higher accuracy observed for face probes (average: 87.7%) than scene probes (average: 83.8%). The main effects of cue type (selection versus non-selection) [$f(1,28) < 1$] and of group (Controls versus MDD) [$f(1,28) = 1.84$, $p = 0.19$] on response accuracy were not significant. When examined in the same manner, a main effect of cue type on reaction time was significant [$f(1,28) = 52.01$, $p<0.0001$], with shorter RTs observed in trials with selection cues (average: 1026.28ms) than non-selection cues (average: 1123.75ms). Main effects of probe type [$f(1,28) = 2.08$, $p=0.16$] and group [$f(1,28) = 2.78$, $p=0.11$] on reaction time were not significant.

Both groups showed a significant benefit for selecting both faces [HC: $t(14) = 4.306$, $p < 0.01$l; MDD: $t(14) = 3.274$, $p < 0.01$] and scenes [HC: $t(14) = 4.306$, $p < 0.01$l; MDD: $t(14) = 2.766$, $p < 0.05$], with the selection benefit slightly higher in the control group for both (faces: mean = 114.93ms, stdev = 101.09ms; scenes: mean = 125.72ms, stdev = 113.08) compared to the MDD group (faces: mean = 85.56ms, stdev = 101.27; scenes: mean = 64.28ms, stdev = 93.12). However, group differences in the behavioral benefit of selecting face [$t(28) < 1$] and scene [$t(28) = 1.63$, $p = 0.12$] stimuli were not significant.

As expected, group differences in scores on the IDS [$t(28) = 10.141$, $p < 0.0001$], RRS [$t(28) = 7.58$, $p < 0.0001$, STAI-Trait [$t(28) = 7.64$, $p < 0.0001$], and STAI-State measures recorded both before [$t(28) = 3.58$, $p < 0.05$] and after [$t(28) = 2.30$, $p < 0.05$] scanning were statistically significant, with the MDD group showing significantly higher scores on each questionnaire compared to controls. Group differences in valence ratings [$t(28) = 1.32$, $p = 0.20$],

post memory scores [$t(28) < 1$], and operation span scores [$t(28) = 1.46$, $p = 0.16$] also did not reach statistical significance. For one subject in the MDD group, post-memory scores could not be obtained because of technical problems. Finally, demographic variables such as education [$t(28) < 1$] and subject age [$t(28) < 1$] did not significantly differ between groups.

2.3.2 Functional Localization of Face- and Scene-Specific Brain Areas (Localizer Results)

The purpose of the functional localizer task was to identify brain regions showing category specific activations towards faces and scene stimuli. In within group analyses, both the healthy control and MDD groups showed significant clusters in face block > scene block and scene block > face block group contrasts ($p<0.001$, FDR corrected at the cluster level, voxel extent ≥ 6). As shown in Table 2.02, face selective clusters for the control group included the right FFA, left and right amygdala, right STS, and cuneus. A cluster in the right OFA also approached significance after FDR correction. In the MDD group, face selective clusters included the right OFA as well as the right and left amygdala. A cluster in the right FFA also approached significance (Figure 2.02a, Table 2.03). As shown in Table 2.04, scene selective clusters in the healthy control group included the left and right PPA, left and right TOS, and left and right RSC. Scene selective clusters for the MDD group included the left and right PPA, the left and right TOS, the left RSC, and the left SPL (Table 2.05).

Between group comparisons demonstrated that the healthy control group showed significantly greater activity in the left superior frontal gyrus in face>baseline contrasts compared to the MDD group (Table 2.06). Between group comparisons of scene>baseline, face>scene, and scene>face contrasts revealed no significant clusters at our statistical threshold ($p < 0.001$, FDR corrected at the cluster level; voxel extent ≥ 6).

2.3.3 Identification and Evaluation of Face and Scene Selective ROIs

As shown in table 2.07, we were successful in identifying face and scene network ROIs in both healthy control and MDD group subjects. Regions in the scene-processing network showed an especially large overlap in comparisons of control and MDD group subjects (see Figure 2.02.). To evaluate group differences in the specificity of face and scene network ROIs, average signal change values were calculated for face and scene blocks for each subject. Using an average of the first two volumes of each block as baseline, percent signal change values were calculated for each subsequent volume (Figures 2.03, 2.06a). Average signal change values extracted from volumes 5-8 of each block (the last 8 seconds of face/scene/object block presentation) were then used to calculate an overall signal change score for each block type. Signal change values for face and scene blocks were then entered into a series of repeated measures ANOVAs designed to test the main effects of group and block type in each region.

As expected, the main effect of block type (face versus scene) was significant in the left [$f(1, 28) = 40.38$, $p < 0.0001$] and right [$f(1, 28) = 92.68$, $p < 0.0001$] FFA, left [$f(1, 28) = 34.30$, $p < 0.0001$] and right [$f(1, 28) = 50.09$, $p < 0.0001$] OFA, right STS [$f(1, 28) = 9.11$, $p < 0.01$], and left [$f(1, 28) = 17.96$, $p < 0.0001$] and right [$f(1, 28) = 31.12$, $p < 0.0001$] amygdala. The main effect of group and interactions between block type and group were not significant for any face network ROI.

For scene network ROIs, the main effect of block type was significant in the left [$f(1, 28) = 89.14$, $p < 0.0001$] and right [$f(1, 28) = 81.14$, $p < 0.0001$] PPA, left [$f(1, 28) = 58.14$, $p < 0.0001$] and right [$f(1, 28) = 50.18$, $p < 0.0001$] TOS, and left [$f(1, 28) = 10.03$, $p < 0.01$] and

right [$f(1, 28) = 27.56$, $p < 0.0001$] RSC. The main effect of group and interactions between block type and group were not significant for any scene network ROI.

2.3.4 Selective Information Processing in Face and Scene-Selective Regions (WM Task Results)

Within and between-group analyses examining clusters showing greater activity during select-face trials than select-scene trials revealed no significant clusters during the stimuli, cue, or probe phases of the WM selection task for either group ($p < 0.001$, FDR corrected at the cluster level; voxel extent ≥ 6). Following FDR correction instituted at the cluster level, one cluster in the somatosensory cortex (peak coordinates: x = 18, y = -31, z = 55; extent; 45 voxels) approached significance ($t = 5.19$, $p = 0.08$) during the delay period in the between-group MDD>controls, Face>Scene contrast.

In within-group comparisons of regions showing increased activity during select-scene trials than during select-face trials (Select-scene>Select-face), specificity for scene stimuli was observed in scene network ROIs during both the cue and probe phases of the WM task for both the healthy control and MDD groups, with significant scene-selective clusters observed during in the post-cue delay period in the control group only. During the cue phase, the healthy control group showed significant clusters ($p < 0.001$, FDR corrected at the cluster level; voxel extent ≥ 6) in the left and right PPA, left and right TOS, and right RSC (Table 2.08) during the cue phase of the WM task. In contrast, following FDR correction, the MDD group showed a significant cluster in the left PPA only. Activations within the right PPA, right TOS, and left RSC also showed supra-threshold activity in MDD group subjects during the cue phase, though these clusters did not survive FDR correction at the cluster level (Table 2.09). During the post-cue delay period, only the control group showed any significant clusters in select-scene>select-face comparisons, with significant clusters observed in both the left and right PPA as well as a cluster within the somatosensory cortex (Table 2.10). During the probe stage, significant clusters in the left and right PPA and left TOS were observed in both groups (Tables 2.11, 2.12), with the MDD group also demonstrating a significant cluster in the right TOS (see Figure 2.04)

Using the average of the first two volumes of each trial as baseline, average percent signal change was calculated for each ROI during the WM task (see figures 2.5, 2.06). Percent signal change for select-face, select-scene, and non-select trials with face and scene probes were calculated for each scan. To examine the main effects of group and cue-type (select-face versus select-scene versus non-selection) during the cue and delay phases of the WM task, average values for each ROI during these phases (scans 5-7 and scans 8-10 respectively) were calculated for each subject and entered into a series of one-way analyses of variance. Similarly, to examine the main effects of group (Controls versus MDD), cue-type (selection versus non-selection), and probe-type (face versus scene) during the probe phase, average values for each ROI were calculated during this stage for each subject (scans 12-14) and entered into a repeated measures ANOVA.

During the cue phase of the WM task, the main effect of group was insignificant for all face network ROIs [$f(1,27) < 1$]. For scene network ROIs, the main effect of group was significant only in the left PPA, which showed significantly greater activity in the MDD group compared than in controls [$f(1,27) = 6.14$, $p < 0.05$]. A main effect of cue (select-face versus select-scene versus non-selection) was insignificant for all face network ROIs and only trended towards significance in the right RSC [$f(2,27) = 2.69$, $p = 0.08$], with this region showing greater activation following select-face and select-scene cues than non-selection cues. Finally, during the cue phase, a significant group by cue interaction was observed to trend towards significance in

the right PPA [$f(2,27) = 2.69$, $p = 0.08$], which showed greater activations following select face and non-selection cues in MDD group subjects than in controls. T-tests directly comparing activity in this region during these conditions were not significant.

During the post-cue delay period, the main effect of group trended towards significance only in the left PPA [$f(1,28) = 4.01$, $p = 0.06$), which showed greater activity in MDD group subjects than controls. The main effect of cue (select-face versus select-scene versus non-selection) was significant in the right FFA [$f(2,27) = 7.83$, $p < 0.01$], with this region demonstrating increased activity during select-face trials than during select-scene and non-selection trials. As expected given previous studies of this area (most notably Oh & Leung, 2010), a main effect of cue-type was significant in the left [$f(2,27) = 3.30$, $p < 0.05$] and right [$f(2,27) = 3.35$, $p < 0.05$] PPA, with increased activity observed in these regions during select-scene trials compared to select-face and non-selection trials. A similar pattern also trended towards significance in the right RSC [$f(2,27) = 2.40$, $p = 0.10$]. Unfortunately, as indicated by Mauchly's Test of Sphericity, comparisons these scene-network regions violated the assumption of sphericity [left PPA: $X^2(2) = 14.56$, $p < 0.01$; right PPA: $X^2(2) = 7.64$, $p < 0.05$; right RSC: $X^2(2) = 11.62$, $p < 0.01$]. With the Huynh-Feldt correction applied, the effect of cue type in these regions was no longer significant [$f < 1$]. No group by cue-type interactions was significant during the delay phase.

During the probe phase, the main effect of group was not significant for any face or scene network ROI. Only the left OFA showed a significant main effect of cue-type [$f(1,28) = 5.77$, $p < 0.05$], with this region showing greater activity during selection trials (select-face and select-scene) than non-selection trials. A similar pattern also trended towards significance in the right TOS [$f(1,28) = 3.72$, $p = 0.06$]. A main effect of probe-type (face versus scene) was significant in multiple face and scene network ROIs. Among face network ROIs, the right FFA [$f(1,28) = 16.18$, $p < 0.0001$] and right STS [$f(1,28) = 5.39$, $p < 0.05$] showed a significant main effect of probe-type, with these regions each showing significantly greater activity in response to face probes than scene probes. This pattern also trended towards significance in the left FFA [$f(1,28) = 3.74$, $p = 0.06$], right OFA [$f(1,28) = 3.48$, $p = 0.07$], left STS [$f(1,28) = 3.56$, $p = 0.07$], and right amygdala [$f(1,28) = 3.73$, $p = 0.06$]. Among scene network ROIs, the left [$f(1,28) = 47.57$, $p < 0.0001$] and right [$f(1,28) = 31.40$, $p < 0.0001$] PPA, left [$f(1,28) = 27.065$, $p < 0.0001$] and right [$f(1,28) = 22.43$, $p < 0.0001$] TOS, and right RSC[$f(1,28) = 6.14$, $p < 0.05$] all showed a significant main effect of probe, with each of these regions showing significantly increased activity in response to scene probes compared to face probes. A similar pattern also trended towards significance in the left RSC [$f(1,28) = 3.34$, $p = 0.08$]. Cue-type (selection versus non-selection) by group (MDD group versus healthy control group) interactions were significant in both the left OFA [$f(1,28) = 4.58$, $p < 0.05$] and right STS [$f(1,28) = 5.40$, $p < 0.05$], with healthy control group subjects showing significantly greater activity during non-selection trials compared to MDD group subjects [STS: $t(28) = 2.75$, $p < 0.05$]. Group by probe-type (face versus scene) and group by cue-type by probe-type interactions were not significant for any ROI during the probe phase.

2.3.5 Selectivity of Face and Scene Network Regions for their Preferred Visual Category

To more precisely quantify group differences in regional selectivity for face or scene stimuli, selectivity index values were calculated each ROI during the functional localizer task and the cue, delay, and probe phases of the WM task for each subject. Group differences in selectivity were then evaluated using a series of independent samples t-tests. The relationship

between selectivity for the preferred visual stimuli and behavioral measures of MDD symptomatology and other behavioral measures were assessed using bivariate correlations

As shown in figure 2.07, group differences in selectivity index values were not significant for any face network ROI during the functional localizer task. In contrast, MDD group subjects showed significantly lower selectivity in several scene network regions-specifically the left PPA [$t(28) = 2.53$, $p < 0.05$], right PPA [$t(28) = 2.34$, $p < 0.05$], and left RSC [$t(28) = 2.07$, $p < 0.05$]. These decreases to be driven by increased activity during face blocks in MDD subjects compared to controls, rather than a decrease during scene blocks. During face blocks, increased activity for MDD subjects compared to controls was significant in the left PPA [$t(28) = 2.18$, $p < 0.05$] and trended towards significance in the right PPA [$t(28) = 1.88$, $p = 0.07$].

During the WM task, a main effect of group on selectivity index was not significant for any face or scene network ROI during the cue, delay, or probe phases except for the left RSC during the probe phase [$t(28) = 2.24$, $p< 0.05$]. Decreased selectivity for the MDD group compared to controls also approached significance in RSC during the delay phase [$t(28) = 1.99$, $p = 0.06$] (Figure 2.12). As shown in figures 2.08, scene network ROIs such at the PPA was highest during the post-cue delay and probe phases for both groups. Selectivity indices for each ROI during the cue, delay, and probe phases for the WM task are summarized in figure 2.09.

2.3.6 Correlations between Regional Selectivity Index and Behavior

For subjects in the MDD group, several notable correlations emerged between selectivity indices calculated during the WM selection task, behavioral measures of working memory performance, and scores on questionnaires measuring MDD symptomatology for subjects in the MDD group. For face network ROIs, selectivity in the left FFA during the post-cue delay period negatively correlated with overall response accuracy [$r(15) = -0.59$, $p < 0.05$]. As shown in figure 2.10a, along with similarly significant correlations in the left [$r(15) = 0.64$, $p < 0.05$] and right [$r(15) = 0.69$, $p < 0.01$] OFA, selectivity in the left FFA [$r(15) = 0.80$, $p < 0.0001$] during the probe stage significantly correlated with the behavioral benefit of selecting face stimuli.

For scene network ROIs, selectivity in the right PPA during the post-cue delay period positively correlated with the behavioral benefit of selecting scene stimuli [$r(15) = 0.63$, $p < 0.05$]). Similar to what was observed in face network ROIs, selectivity in the left PPA also correlated with the benefit of selecting scene stimuli $r(15) = 0.52$, $p < 0.05$ during the probe stage (Figure 2.10b). Selectivity in the left PPA [$r(15) = 0.63$, $p < 0.05$] and right TOS [$r(15) = 0.54$, $p < 0.05$], during the delay phase positively correlated with overall response accuracy.

Finally, as shown in figure 2.10c, selectivity indices in several scene network ROIs also negatively correlated with IDS score. In the left PPA [$r(15) = -0.53$, $p < 0.05$] and right RSC [$r(15) = -0.61$, $p < 0.05$], selectivity indices negatively correlated with IDS score during the post-cue delay phase, with no significant correlations observed in these regions between selectivity indices and any measure of disease severity or symptomatology during the cue and probe phases.

2.4 Chapter Discussion

In the present study, we investigated the effect of major depressive disorder (MDD) on information processing in brain regions associated with the selective processing of face and scene stimuli. In these regions, MDD group subjects showed a similar pattern of activity during the functional localizer and WM selection tasks as healthy control subjects, insofar as both

groups showed the same stimuli-specific activity observed in previous studies (e.g. Epstein et al., 1998; Kanwisher et al., 1997; Lepsien & Nobre, 2007; Oh & Leung, 2010). Between group differences were observed primarily in the selectivity exhibited within face and scene selective regions.

Contrary to our initial hypothesis, MDD-related disruptions in selective information processing were significant, primarily, in brain regions investigated for their role in the selective processing of scenes- most notably the parahippocampal place area (PPA) and retrosplenial cortex (RSC)- rather than in regions involved in face processing. However, because decreases in selectivity in these regions were related to increased signal change in response to select-face cues (rather than decreased signal change during select-scene cues), these findings indicate that the processing of faces may be significantly, if not uniquely, disrupted in MDD.

2.4.1 The PPA and RSC: Beyond Selective Scene Processing

The results of our analyses could be interpreted in the context of studies investigating the influence of emotion on information processing. Converging evidence from behavioral and fMRI studies suggest that the processing of non-face visual information, even in healthy subjects, may be significantly influenced by emotional context. For example, a series of studies by Bocanegra and Zeelenberg (2007; 2009) demonstrated that the presentation of negative faces impairs later visual perception. Specifically, the presentation of a negative (fearful) face impairs later perception of high spatial frequency targets and appears to enhance the perception of low frequency targets (Bocanegra & Zeelenberg, 2009). Work by Schmitz and colleagues (2009) indicate that these differences may relate to disruptions in brain regions analogous to the scene-network ROIs in the present study. When presented with sad faces, healthy subjects showed a decreased response within the parahippocampal gyri in response to peripherally presented scene stimuli compared to scenes presented alongside happy or neutral faces (Schmitz et al., 2009). However, though our valence rating task was a (relatively) coarse measure of how MDD and healthy control subjects perceived the emotional content of the visual stimuli employed in the present experiment, the absence of significant between-group differences on any behavioral metric indicates that any explanation of our findings based only on between group differences in emotion perception is insufficient.

In parallel to research indicating a link between emotional context and activity in scene-selective brain regions, a burgeoning body of work has demonstrated the involvement of the parahippocampal gyrus and retrosplenial cortex in memory encoding and retrieval (for review, Brown & Aggleton, 2001; Squire et al., 2004; Ranganath & Ritchey, 2012; Van Strian et al., 2009). Source memory studies have demonstrated a reliable correlation between increased BOLD activity in the parahippocampal gyrus during memory encoding and retrieval and later successful recollection of contextual information (Davachi et al., 2003; Ranganath et al., 2004; Diana et al., 2007). Likewise, the RSC appears to show increased activity during the retrieval of contextual information, though its role in the encoding of context is, thus far, unclear (Daselaar et al., 2009; Johnson et al., 2009; Yanelinas et al., 2005) Because of these results, several researchers have proposed that these regions primarily subserve contextual processing rather than just the selective processing of scenes (Bar et al., 2007; 2008; Epstein et al., 2008).

In addition to their role in scene and contextual processing, the parahippocampal gyrus and retrosplenial cortex have also been shown to be involved in social cognition, with a recent meta-analysis demonstrating that clusters within the PPA and RSC observed to be active during memory tasks largely overlap with those active during theory of mind tasks (Spreg et al., 2009).

In a recent review, Ranganath and Ritchey (2012) synthesized the memory, perceptual, and social functions of the PPA and RSC (as well as the perirhinal cortex) into a comprehensive model concerning the neural basis of memory-guided behavior. This model includes two anatomically and functionally distinct sub-systems: the posterior medial system, which includes the parahippocampal and retrosplenial cortices, and appears to be involved in forming situational models and the anterior temporal system, which includes the orbito-frontal cortex and amygdala, and appears to be involved in assessing salience (Ranganath & Ritchey, 2012).

2.4.2 MDD and the Posterior Medial System

The results of the present study could be interpreted as evidence for a specific deficit in the processing of visual scenes during MDD. However, this is unlikely given the robust literature demonstrating other cognitive and social deficits during the disease. For example, subjects with MDD report significantly fewer specific and autobiographical memories when prompted than controls (Vam Vreeswojk & de Wilde, 2004), a difference that is reflected by significantly decreased activity within the hippocampal and parahippocampal gyri during the recall of autobiographical memories (Young et al., 2012). Furthermore, in addition to memory-related difficulties, depressed subjects also show significant deficits in theory of mind (McCullough, 2003) and significantly decreased sensitivity to context whole engaging in emotional processing (Rottenberg et al., 2005)- all of which is more consistent with a disruption in brain regions involved in the generation of situational models than in those associated with simply the processing of scenes (or, for that matter, faces).

Subjects with MDD have often been found to have significant difficulties in situations in which their behavior is not structured or constrained by task rules (e.g. Hertel & Rude, 1991; for review, Hartlage et al., 1993; Hertel, 1998). These findings have often been linked to MDD-related deficits in inhibition (see Gotlib & Joormann, 2010) or an overall decrease in "cognitive resources" (see Burt et al., 1995). However, because unconstrained situations often require cognitive flexibility, goal-driven behavior, and cognitive control (Hertel, 2004), such deficits could also arise from a more general difficulty in the generation of situational modals rather than deficits specific to just cognitive inhibition or cognitive resources.

Though the complexity of MDD symptoms implies that the disease likely affects functioning in brain regions beyond just those in the posterior medial system as defined by Ranganath and Ritchey (2012), the results of the analyses described in this chapter do support a link between the breadth of cognitive deficits observed during the disease and MDD-related disruptions in regions involved in generating appropriate situational models. Though we initially predicted that the processing deficits present in MDD would be unique to face stimuli and would be reflected in disruptions primarily in the face-processing network, our findings are indicative of a much broader disruption in cognitive processing, of which, perhaps owing to their strong social and emotional content, disruptions related to the processing of faces may be only the most obvious at the behavioral level.

2.4.3 Face Processing Difficulties in MDD (Revisited)

In line with current hypotheses regarding category specific activations in visual association regions including (for review, Haxby et al., 2010; Nasr et al., 2011) and studies indicating that subjects with MDD may have a particular difficulty in the processing of face stimuli (for review, Hamilton & Gotlib, 2008; Stuhrmann et al., 201), we hypothesized that MDD-group subjects would show significant (and specific) disruptions in face-selective brain

regions including the fusiform (FFA) and occipital (OFA) face areas and superior temporal sulcus (STS). Instead, our results lent support to our alternative hypothesis- that MDD would be associated with a more general disruption evident in both the face and scene processing networks.

While the analyses described in this chapter demonstrated a disruption in scene selective regions in subjects with MDD compared to controls, we also found indications for disruptions in face-processing regions. As previously noted, between-group differences in regional specificity or selectivity did not reach statistical significance for any ROI in the face processing network during either the functional localizer or the WM selection task. However, as shown in figures 2.15 and 2.17, the MDD group showed lower selectivity index values in the right FFA and bilateral OFA during the delay phase of the WM task than control subjects. Though these decreases were not statistically significant, because similar decreases in scene-selective ROIs also failed to reach statistical significance, it is possible that the (relatively) low sample size used in the current analyses masked a disruption in these regions that may be more subtle than the disruptions observed in scene network ROIs.

Stronger evidence for MDD-related disruptions in face-selective regions comes from the significant correlations observed between selectivity index values and measures of behavioral performance. The presence of a significant positive correlation between selectivity index values during the post-cue delay period and the behavioral benefit of selecting face stimuli in the left FFA in MDD group subjects, as well as the significant correlations between selectivity at the probe stage and overall response accuracy in the left FFA and bilateral OFA, point to a relationship between MDD-related difficulties in performance on the WM task and the specificity of activity in these regions.

A recent study designed to examine patterns of neural activity predictive of a treatment response to the muscarinic receptor antagonist scopolamine has indicated a significant relationship between treatment response and activity in the bilateral middle occipital cortex (MOC) in subjects with MDD (Furey et al., 2013). In this study, a negative correlation was observed between MOC activity during the WM task prior to treatment and treatment response. After treatment, a positive correlation was observed. Though correlations between symptom severity and regional selectivity were only significant in regions in the scene processing network in the present study, Furey et al.'s findings related to disrupted activity following the processing of face stimuli lend converging evidence that MDD likely also disrupts regions involved in face processing. Though selectivity indices in face network regions did not significantly correlate with measures of disease severity, as they did in the PPA and RSC, the results described in this chapter point to a link between disruptions in face processing regions and MDD-related declines in behavioral performance that should be investigated in future studies.

2.4.4 Future Directions

Interpreting the findings of the present study as evidence for significant disruptions within a network that includes the PPA and RSC during MDD, does not and should not, diminish the importance of work showing MDD-related disruptions in other brain regions. MDD involves disrupted activity in a broad range of cortical and subcortical regions (e.g. Mayberg. 1997; 1999). Though the present study indicates that there is disruption detectable within the "scene-processing network," it is extremely likely that such disruption is related to disruptions elsewhere- including in the PFC and the amygdala.

Though the present study indicates that MDD-related disruptions in visual processing are not limited to deficits in face processing, these results open several new questions regarding the neural basis of cognitive deficits in MDD. Of these, questions regarding the relationship between the disruptions observed in the present study and activity in the wider brain circuit supporting working memory (WM) are addressed in the analyses described in the next chapter. Further questions, related to the use of emotionally valenced stimuli, broader subject populations, and more advanced research techniques, should be addressed in future studies.

Emotionally neutral stimuli were used in the present study to investigate cognitive disruptions unrelated to the type of emotion regulation deficits commonly observed in subjects with MDD (Oschner & Gross, 2005). While this approach allowed us to detect dysfunction in a broad network of brain regions, it precluded us from investigating the interaction between emotion regulation and selective information processing. Evidence from work with healthy subjects indicates that negative stimuli could exacerbate the types of disruption observed in the present study (Bocanegra & Zeelenberg, 2009; Schmitz et al., 2009). However future research, using strongly valenced as well as emotionally neutral stimuli, is required to empirically examine this link in subjects with MDD compared to controls.

Because of practical constraints in subject recruitment, subjects in the present study were drawn from a relatively narrow demographic sample, consisting of relatively young and relatively well-educated participants, with MDD group subjects experiencing relatively mild symptoms. In the broader population, the symptoms of MDD are quite heterogeneous and likely interact with a large number of demographic variables (Carragher et al., 2009) outside the bound of the present study. However, correlations between selectivity index values and measures of behavioral performance and MDD symptoms indicate a close link between the severity of disruptions like those observed in the present study and demographic variables. Future studies are needed to delineate how the disruptions observed in the present study are affected by variables including disease etiology, symptom severity, medication status, and subject age. Studies examining the effect of subject age may be most pressing given findings indications of age-related decreases in specificity (age-related dedifferentiation) in both prefrontal and hippocampal regions (Giovanello & Schacter, 2011) and regions examined as part of the face and scene networks, (Park et al., 2004; Park et al., 2010). Furthermore, because the cognitive dysfunction observed in laboratory experiments does not easily map onto the type of cognitive dysfunction experienced by depressed individuals in their daily lives (Baune et al., 2010), future studies will be needed to assess how the results of the present study relate to dysfunction in more naturalistic settings- where selective information processing occurs alongside a multitude of other processes.

The present study was designed to investigate the neural basis of MDD-related deficits in selective information processing. Unfortunately, such deficits may occur at a scale not detectable by the techniques used. A region of interest (ROI) approach was used in the present study because of its utility in examining activity in functionally defined brain regions (e.g. the FFA and PPA) (see Poldrack, 2007), however this approach has several limitations. Perhaps the most widely cited criticism of using ROIs is that their use severely restricts the focus of researchers examining phenomena that may arise from activity in distributed networks of brain regions (see commentary by Friston et al., 2006). Essentially, the concern is that by focusing on relatively a relatively small number of regions, researchers will miss this larger picture of what is occurring in the brain. In general, researchers have overcome this limitation by using ROIs alongside a repertoire of other analysis techniques (Saxe et al., 2006). The analyses discussed in the next

chapter were carried out, partially, for this purpose. To examine how MDD affects activity WM processing in regions beyond just the face and scene-processing network, these analyses investigated how the disease affects functioning in regions throughout the entire brain. However, even beyond the techniques discussed in the next chapter, relatively new forms of analyses could be applied to the study of the effect of MDD on the face and scene-processing regions. Work using multi-variate pattern analysis (MVPA) has shown that spatial response patterns indicative of the selective maintenance of face and scene stimuli can be detected in both the FFA and PPA during the cue phase of a paradigm very similar to the one used in the present study (Han et al., 2013). Future research using this technique is necessary to establish whether the results of the present study are due to the relatively low resolution of the methods used or if these results are indicative of disruptions also present at the level of pattern classification.

Chapter 3

Major depressive disorder (MDD) is associated with disrupted activity in brain regions associated with WM selection

3.1 Chapter Introduction

Beyond deficits specific to emotionally or socially relevant stimuli (such as human faces), there is growing evidence from behavioral and neuroimaging studies that MDD may be related to disruptions in component cognitive processes such as the maintenance and selection of information held within working memory (WM) (for review, Austin et al., 2001; Clark et al., 2009; Hammar & Ardal, 2009; Mathews & MacLeod, 2005; Thomas & Elliott, 2009). In addition to the disruptions discussed in the previous chapter, MDD has been shown to significantly affect functioning in a number of brain regions involved in information processing including the cingulate cortex (e.g. Matthews et al., 2009; Mitterschiffthaler et al., 2003), the thalamus (e.g. Fu et al., 2005), the hippocampus (e.g. Werner et al., 2009), the basal ganglia (e.g. Robinson et al., 2012), the amygdala (e.g. Fales et al., 2008; Lee et al., 2008), and regions within the orbitofrontal, lateral, and medial prefrontal cortices (e.g. Mayberg,1999; 2003). While studies directly examining WM-related deficits have demonstrated disrupted activity in some of these same brain regions, the directionality and strength of such disruptions have proven to be quite heterogeneous (for review, Fitzgerald et al., 2008; Price & Drevets, 2010). For example, while disrupted activity in the lateral prefrontal cortex (lPFC) has often been reported, both hyper- and hypoactivity in clusters within this region have been observed in subjects with MDD compared to controls (for review, Fitzgerald et al., 2006).

This heterogeneity likely arises from several sources. In work with healthy subjects, individual differences in variables including subject age (e.g. Rajah & D'Esposito, 2005) and working memory capacity (e.g. Osaka et al., 2007) as well as study design parameters such as the presentation time of study stimuli and trial ordering (see Witt et al., 2013) have been shown to significantly affect the results of neuroimaging studies examining cognitive processing. When combined with additional sources of variability, such as the medication status of MDD-group subjects (e.g. Anand et al., 2005; Hamilton et al., 2008; Sheline et al., 2001), the potential for significant differences between study populations can complicate the interpretation of between group comparisons conducted within- and between studies comparing MDD and control group subjects. Partially owing to this complexity, it is presently unclear how MDD affects activity in the congregation of brain regions that support component cognitive processes including those involved in the selection and maintenance of information in WM. Disentangling precisely how differences in subject characteristics and study parameters contribute to the heterogeneity in the results of studies examining MDD-related cognitive deficits is beyond the scope of the analyses described in this chapter. Instead, these analyses were intended to investigate the effect of the disease on WM selection and maintenance in such a way as to either control for, or directly evaluate the effect of, individual differences while using task parameters previously drawn from a previous investigation of these processes in healthy subjects (Oh & Leung, 2010).

As noted in chapter one, the prefrontal cortex is a logical target for examining MDD-related dysfunction in WM, owing to its role in emotion regulation (Oschner & Gross, 2005) and executive control (Miller & Cohen, 2001). Indeed, the PFC has long been examined for its role in instantiating WM in healthy subjects (see Fuster, 1973; 2008; Goldman-Rakic, 1987; 1990; Goldman-Rakic & Leung, 2002). Early conceptions of the PFC as a major site of WM

maintenance were derived from single unit electrophysiological studies showing sustained delay period activity in PFC neurons in non-human primates (e.g. Funahashi et al., 1989; 1993b; Wilson et al., 1993) and from neuropsychological studies demonstrating a robust link between lesions in the PFC and disruptions in WM task performance (e.g. Funahashi et al., 1993; Petrides & Milner, 1981). Converging evidence from recent electrophysiological studies involving non-human primates and neuroimaging studies involving human subjects have demonstrated that, rather than being the major site of WM maintenance, the PFC contributes to the control WM through biasing activity in brain regions with which it has strong functional and anatomical connections, including visual association regions (Ungerleider et al., 1998) the premotor cortex (Petrides et al., 1993), and clusters throughout the temporal, occipital, and parietal cortices (Jonides et al., 2008; Miller & Cohen, 2001; Postle, 2006; Ranganath & D'Esposito, 2005).

Neuroanatomical work with non-human primates has demonstrated that the medial and lateral aspects of the PFC can be characterized by their strong reciprocal connections with different groups of brain regions. The lateral PFC has strong connections with multiple regions believed to be involved in WM processing, including regions within the sensory association cortices and the posterior parietal lobe (Pandya & Seltzer, 1982; Petrides & Pandya 1984; 1988; 1999). In contrast, the medial PFC has strong connections with regions in the limbic system, including the amygdala (Barbas, 1988; Barbas & De Olmos, 1990; Carmichael & Price, 1995; 1996). Because of these differences (see also, Cavada and Goldman-Rakic, 1989; Barbas, 2000; Xiao & Barbas, 2006; 2006b), the dorsolateral (dlPFC) and ventromedial (vmPFC) aspects of the PFC are often investigated for their roles in "executive" and "emotional" functions respectively. Research examining the neural basis of processing deficits in MDD has tended to follow this model, with some models of the disease postulating that MDD symptoms may be associated with an overall hyperactivity in the vmPFC and hypoactivity in the dlPFC. Such disruptions are believed to be related to the increased generation of negative affect and disruptions in executive control observed during the disease (review, Koenigs & Grafman, 2008; Murrough et al., 2011).

As noted in sections 1.1.1. and 1.2.3., many researchers have used a variant of the *n*-nack task (Braver et al., 1997 Owen et al., 2005) to examine WM disruptions in subjects with MDD (see also Diener et al., 2007; Fitzgerald et al., 2008). Studies using this task have often demonstrated disrupted patterns of activity in the lateral and medial PFC in subjects with MDD compared to controls (Barch et al., 2003; Garett et al., 2011; Harvey et al., 2005; Matsuo et al., 2007; Rose et al., 2006; Walsh et al., 2007; Walter et al., 2007). However, possibly due to differences in study parameters including stimuli-type (e.g. letters versus human faces) or presentation times (e.g. 500ms versus several seconds) as well as subject characteristics between studies, the directionality of these disruptions has been largely heterogeneous.

Beyond studies using *n*-back tasks, a relatively small number of studies have investigated MDD-related disruptions in WM-related brain regions beyond the vmPFC and dlPFC. A paradigm allowing researchers to examine the neural correlates of WM load has recently been used in a series of studies designed to investigate MDD-related disruptions in WM-related brain regions (Wolf & Walter, 2005; Walter et al., 2007; 2007b; Vasic et al., 2009). When compared to matched controls, subjects with MDD have been found to exhibit increased activity in the dorsolateral PFC (alongside decreased response accuracy) compared to controls while completing a delayed match to sample task. In a follow-up study using the same paradigm, decreased functional connectivity has been observed between the dorsolateral PFC and regions in the parietal cortex in depressed subjects compared to healthy controls (Vasic et al., 2009).

In parallel, a line of research with healthy subjects has shown that activity in the posterior parietal cortices, specifically the intraparietal sulci (IPS), is closely linked to capacity limitations in visual working memory (Leung et al., 2004; Linden et al., 2003; Todd & Marois, 2004). As discussed in section 1.1.1, such capacity limitations make it necessary that the contents of WM be updated efficiently. At the neural level, several regions have been studied for their role in WM control. The ventrolateral PFC, a region that has generally not been the focus of studies examining the neural basis of MDD symptoms, has been shown to be important for the selection and controlled retrieval of information within WM (Badre et al., 2005) and the resolution of (proactive) interference (Badre & Wagner, 2005; Nee et al., 2007; for review, Badre & Wagner, 2007; Jonides & Nee, 2006). Similarly, the basal ganglia- a region that has been widely investigated for its role in instantiating MDD symptoms (Lacerda et al., 2003; Lorenzetti et al., 2003), has also been shown to play an important role in allowing only relevant information access to working memory (Frank et al., 2001; McNab & Klingberg, 2007). Taken together, brain regions including the posterior parietal cortices, the VLPFC, and the basal ganglia do not just represent additional targets for examining MDD-related disruptions in WM, but are also indicative that MDD-related deficits in WM likely arise from dysfunction in a broader selection of WM-related brain regions than has been addressed is previous studies.

The analyses described in the remainder of this chapter were designed examine the effect of MDD on the (relatively) broad congregation of brain regions that support working memory processes including selection and maintenance. As previously noted, multiple studies have examined the neural basis of WM dysfunction in MDD. However, many of these studies (e.g. Barch et al., 2003; Garett et al., 2011; Harvey et al., 2005; Matsuo et al., 2007; Rose et al., 2006; Walsh et al., 2007; Walter et al., 2007) have used task paradigms that require the simultaneous use of multiple WM processes simultaneously. For example, though the n-back task has been used in many studies to investigate the neural basis of WM processing (see Owen et al., 2005), it requires subjects to select and maintain task relevant information simultaneously- making it difficult to disentangle activity to each individual process. In contrast, though the WM selection task used in the present study has both selection and maintenance components, they are present at discrete points during each trial. Using this task we were able to examine both selection and maintenance-related activity in MDD group subjects compared to healthy controls. In addition, we were able to perform some exploratory analyses examining how variables such as WM task performance and disease severity relate to dysfunctional activity related to both processes.

3.2 Methods

Each of the analyses described in this chapter used behavioral and imaging data collected during the procedure described in chapter two (see sections 2.2.1-2.2.8). The same thirty subjects (15 unmedicated subjects with MDD, 15 matched controls) were included in each of the analyses described in this chapter as in the analyses described in chapter two. All behavioral measures of WM-task performance and MDD symptomatology were identical to those summarized in table 2.01. As described in section 2.2.1, healthy control and MDD group subjects were matched in terms of age [$t(28) < 1$] and education [$t(28) < 1$], with no significant differences on operation span scores [$t(28) = 1.32$, $p = 0.20$], and valence ratings for study stimuli [$t(28) = 1.32$, $p = 0.20$]. Similarly, performance measures on the WM selection task, including overall response accuracy [$t(28) = 1.61$, $p = 0.12$], average reaction time [RT: $t(28) < 1$], and the behavioral benefits of selecting both face [$t(28) < 1$] and scene stimuli [$t(28) = 1.63$, $p = 0.12$] did not significantly

differ between groups. As expected, measures of symptom severity including IDS [$t(28) = 10.141$, $p < 0.0001$] and RRS [$t(28) = 7.58$, $p < 0.0001$] were observed to be significantly different between groups, with the MDD group showing significantly higher scores on all such measures.

As in chapter two, all preprocessing and statistical analyses were conducted using SPM8 (Wellcome department of Cognitive Neuroscience, London, UK; www.fil.ion.ucl.ac.uk/spm). Functional images were corrected for differences in slice timing, high resolution images were segmented into gray and white matter and co-registered to the mean functional image, images were normalized to the MNI gray matter template, and all functional images were smoothed with a 6mm FWHM Gaussian kernel. After preprocessing, image distortion errors caused by scanner spikes were repaired via interpolation from the nearest unaffected volumes using the ArtRepair toolbox (Mazaika et al., 2005). For more details regarding our general experimental procedure and imaging processing parameters, refer to sections 2.2.4-2.2.8.

All of the analyses discussed in the following sections drew upon data from the working memory selection task described in section 2.2.4. (see Figure 2.01b). Onset times for the presentation of the four task evens (stimuli onset, cue onset, post-cue delay, and probe onset) were defined in the same matter as described in section 2.2.8. A series of t-tests were conducted at the individual level to examine activity related to each task event, cue type, and probe-type for each subject individually. Brain activity related to WM maintenance and selection was examined for each individual subject, both by examining activity in selection trials (select-face + select-scene) compared to non-selection trials and by examining activity related to each stimulus category (select-face versus select-scene) compared to non-selection trials. Individual contrast images were then included in second level group analyses. As in chapter two, clusters were first examined at a pre-specified threshold ($p < 0.001$, voxel extent: 6) before the institution of FDR correction. Clusters observed at this threshold were considered statistically significant only if they survived FDR correction at the cluster level (see Chumbly & Friston, 2008; Friston et al., 1991; 1995; Genovese et al., 2002).

3.2.1 Region of Interest Definition

To facilitate a comparison between (potential) MDD-related disruptions in the present study and WM-related activations observed in studies of healthy subjects, we used a series of ROIs drawn from previous studies of spatial working memory conducted by our laboratory (e.g. Leung et al., 2002; 2005) (see table 3.19 for coordinates). As in chapter two, all ROIs were extracted from each subject individually using the Marsbar toolbox for SPM (Brett et al., 2002; http://marsbar.courceforge.net). In line with previous studies, ROIs were constructed with a radius of 10mm. Average time-courses were constructed for each time point of the WM selection task for both groups. Using the first two scans as baseline, average signal change values were then calculated for the stimuli, cue, delay, and probe phases of trials of each cue condition (select-face, select-scene, and non-selection).

3.2.2 Correlation Analysis

To explore how individual differences in working memory task performance and MDD symptomatology relate to disruptions in WM-related brain activity, a series of whole brain correlations were conducted to reveal clusters of activity that significantly correlated with response accuracy on the WM task, operation span scores, the behavioral benefit of selecting face and scene stimuli, and scores on questionnaires measuring MDD symptomatology. Because

scores on the working memory task, operation span task, and measures of the behavioral benefit of selection did not significantly differ between groups, whole brain correlations were conducted in two separate analyses; one in which all MDD and healthy control group subjects were pooled together and another in which subjects from the two groups were analyzed independently. Because group differences in scores on the IDS, RRS, and STAI were so large (see table 2.01), any whole brain correlations conducted with all subjects pooled together would likely result from group-level differences rather than differences between individual subjects within each group. For this reason, whole-brain correlations examining these variables were conducted only on the two groups separately.

3.3 Results

Analysis of activity related to each WM task event demonstrated that the MDD group showed significant disruptions in regions related to the control of WM both prior to and following the onset of the selection cue. During the cue phase, within group comparisons revealed strikingly different groups of brain regions more active in selection trials than in non-selection trials in the two groups. While control group subjects generally showed significant clusters in brain regions previously hypothesized to support WM processing, subjects in the MDD group showed significant selection-related activity mainly in medial temporal regions such as the cuneus. Analyses of a priori regions of interest lent convergent evidence for a widespread disruption in WM-related brain regions in MDD group subjects, with MDD group subjects showing significantly decreased activity in a large number of regions implicated in WM processing during the post-cue delay period. Finally, correlation analyses indicated that selection-related activity in the cuneus among MDD group subjects significantly related both to measures of behavioral performance (i.e. response accuracy and selection benefit) but also to measures of symptom severity (i.e. IDS score).

3.3.1 Within- and Between-Group Activations Related to Each Working Memory Task Event

To examine similarities and differences in WM-related activity in control and MDD-group subjects, we first examined activity during the four basic task events (stimuli presentation, cue presentation, post-cue delay period, and probe presentation) with all cue conditions pooled together. As shown in figure 3.01, healthy control and MDD group subjects showed largely overlapping patterns of activity during the stimuli, cue, and probe phases, though distinct patterns of activity were observed in within group analyses during each study event, most notably the post-cue delay period (Figure 3.01c).

During the stimuli phase, both groups showed large clusters of activity in the occipital, parietal, frontal, and temporal cortices as well as numerous subcortical areas (see figure 3.01). From visual inspection, large clusters in the middle and inferior frontal gyri were significant in the healthy control group, and not the MDD group, during this phase (Table 3.01a). In contrast, a large cluster in the somatosensory cortex was evident in the MDD group that was not supra-threshold in the control group (Table 3.05).

During the cue, phase, both the MDD and control groups showed significant clusters in regions within the prefrontal cortex (Figure 3.01b). From visual inspection, clusters in the posterior parietal posterior lobe (specifically the left SPL) and the anterior cingulate were observed following FDR correction in the control group but not MDD group (Table 3.02). In

contrast, a large cluster was again shown to be significant in the somatosensory cortex in the MDD group only (Table 3.06).

The post-cue delay phase showed the most obvious difference between the healthy control and MDD groups when all study conditions were pooled together (see Figure 3.01c). During this delay period, multiple significant clusters were observed in the prefrontal and posterior parietal cortices for the healthy control group (Table 3.03). These regions have been observed in multiple previous studies using a similar design (see Lepsien et al., 2007; Oh & Leung, 2010). In contrast, the MDD group showed a relatively restricted pattern of activity during the delay period, mainly restricted to small clusters in the prefrontal cortex (Table 3.07).

Finally, during the probe phase, visual inspection revealed that the two groups again showed significant activity in multiple very large clusters encompassing regions throughout the brain (Tables 3.04, 3.08, Figure 3.01d)

Observations of differences in the patterns of activity evoked during the four task events in within groups analyses were supported by the results of between group comparisons. As shown in figure 3.02a, with all conditions pooled together, increased activity during the stimuli phase, in a cluster in the left ventrolateral prefrontal cortex (vlPFC) trended towards significance ($p = 0.06$) following FDR correction in the direct contrast of the healthy control group compared to the MDD group (table 3.09). A similar effect also trended towards significance during the post-cue delay phase ($p=0.06$, FDR corrected), as did a cluster in the left dorsolateral PFC ($p=0.06$, FDR corrected) (Figure 3.02a, Table 3.10). Notably, each of these clusters reached significance ($p\leq0.05$) if multiple comparisons were corrected using a family-wise error (FWE) correction rather than a false discovery rate (FDR) correction. Even when examined at a lower statistical threshold ($p<0.001$, uncorrected), activity in these clusters did not appear to be significantly greater in the control group during the cue and probe phases. As shown in figure 3.02b and table 3.11, with all cue conditions pooled together, the MDD group showed supra-threshold (and significant following FDR correction) activity in a large cluster within the somatosensory cortex than the control group. Notably this cluster was localized near the cluster that trended towards significance during the post-cue delay period in the MDD group>healthy controls select-face>select-scene comparison mentioned in chapter two. Examination of contrast maps as a lower statistical threshold ($p<0.001$, FDR uncorrected) revealed no other region significantly more active in MDD group subjects in stimulus, delay, and probe phases.

3.3.2 Non-Specific Activations during Selective Information Processing (Within-Groups)

As shown in figure 3.03, the MDD and control groups showed significantly different patterns of activity in conjunction analyses examining clusters showing activity during the cue and delay periods across all three conditions (Select-face, Select-scene, Non-selection. As demonstrated in figure 3.03a, with all subjects pooled together, significant clusters were observed in multiple frontal, parietal, and temporal lobe regions during the cue phase- including the anterior PFC, several regions within the lateral PFC, and the bilateral parahippocampal gyri (Table 3.12). During the delay phase, with all subjects pooled together, significant clusters were observed mainly within the prefrontal cortex (Table 3.13). Conjunction analyses conducted on the MDD and control group subjects separately revealed that the majority of clusters observed in the previous analyses were primarily driven by the healthy control group. During both the cue and delay phases, the healthy control group showed similar clusters than in analyses with all subjects pooled together (Figure 3.03b). In contrast, the MDD group showed severely restricted activations during both phases (Tables 3.14, 3.15).

3.3.3 Specific Activations during Selective Information Processing (Within-Groups)

Between-group comparisons of task events separated by cue condition revealed that group differences during the stimuli, cue, and delay phases of the WM task were driven by difference related to conditions of the selection demand imposed by the cue. Though between group analyses did not reveal any clusters significantly more active in either group during selection-related comparisons examining either selection in general (Select-Face + Select-Scene > Non-selection) or the selection of a specific stimulus category (Select-face > Non-selection, Select-scene > Non-selection), within-group analyses demonstrated that the two groups exhibited very different patterns of selection-related activity during the cue phase.

In within-group analyses examining overall selection-related activity during the cue phase (Select-face + Select-scene > Non-selection), the healthy control group showed significant activity in the left IPL, cerebellum, anterior cingulate, precentral gyrus, and caudate nucleus during the cue stage (Table 3.16). In contrast, in the same comparisons, the MDD group showed significant activity primarily in the cuneus and superior temporal gyrus (Table 3.17) (Figure 3.04a).

In select-face versus non-selection comparisons, only the control group showed any significant clusters after FDR correction (Figure 3.04b). In select-face>non-selection contrasts, significant clusters were observed in the left IPL, precentral gyrus, and cerebellum during the cue phase (Table 3.18), Non-selection>select-face comparisons revealed significant clusters in the precuneus, left retrosplenial cortex, and the left parahippocampal gyrus for the control group only (Table 3.19). No significant clusters were observed in select-face versus non-selection comparisons during the delay or probe phases for either group.

In select-scene>non-selection contrasts, the control group showed significant clusters in a number of regions including the anterior and middle cingulate, left dorsolateral PFC, caudate, putamen, cerebellum, precuneus, and middle temporal lobe during the cue phase (Figure 3.04c, Table 3.20). By comparison, the MDD group showed significant clusters mainly in the cuneus, precuneus, cerebellum, and ventral STS (Table 3.21). In similar comparisons examining activity at the probe stage, the healthy control group showed significant clusters in the left and right transverse occipital sulcus, left and right parahippocampal gyrus, and left and right sulcus during the cue phase (Table 3.22), while the MDD group showed significant clusters in the left caudate, right transverse occipital sulcus, anterior PFC, the posterior parahippocampal gyrus, and the right and left retrosplenial cortex (Table 3.23). Only the control group showed any significant clusters in any non-selection>select-scene contrast, with a significant cluster observed in the superior temporal gyrus during the probe phase.

3.3.4 Selection-Related Activity in A Priori Regions of Interest

To relate the MDD-related dysfunction in WM-related brain activity implied by the results discussed in the previous chapter (and sections 3.3.1-3.3.2 of this chapter), we extracted a number of regions of interest drawn from previous WM studies conducted in our laboratory. The first series of ROIs was drawn from studies investigating the neural basis of spatial working memory (Leung et al., 2002; 2005). A list of these ROIs and their coordinates is given in table 3.28.

As expected given the results discussed in the preceding sections, the main effect of group was observed in multiple regions associated with working memory processing. During the stimuli phase, significantly greater activity was observed in the left SFS for the healthy control

group compared to the MDD group [$f(1, 28) = 8.85$, $p < 0.01$]. During the cue phase, significantly greater activity in the left SFS was again observed in the left SFS [$f(1, 28) = 8.85$, $p < 0.01$] for healthy controls compared to MDD group subjects. During the delay phase, the control group showed significantly increased activity in the left SFS [$f(1, 28) = 5.31$, $p < 0.05$], left IPS [$f(1, 28) = 4.59$, $p < 0.05$], and cerebellum [$f(1, 28) = 6.45$, $p < 0.05$] compared to the MDD group, with a similar pattern in trending towards significance in the left MFG [$f(1, 28) = 3.96$ $p < 0.06$]. Finally, during the probe phase, the control group showed significantly increased activity in a number of brain regions involved in WM including the left SFS [$f(1, 28) = 11.25$ $p < 0.01$], left [$f(1, 28) = 15.21$ $p < 0.01$] and right MFG [$f(1, 28) = 5.41$ $p < 0.05$], right premotor, [$f(1, 28) = 4.41$ $p < 0.05$], right SMA [$f(1, 28) = 14.75$ $p < 0.01$], right ACC [$f(1, 28) = 7.28$ $p < 0.05$], left [$f(1, 28) = 11.42$ $p < 0.05$] right [$f(1, 28) = 4.62$ $p < 0.05$] IPS, left [$f(1, 28) = 10.76$ $p < 0.01$] and right [$f(1, 28) = 7.76$ $p < 0.05$] IPL, left SPL [$f(1, 28) = 8.83$ $p < 0.01$], left MOG [$f(1, 28) = 6.18$ $p < 0.05$], basal ganglia [$f(1, 28) = 9.51$ $p < 0.01$], right thalamus [$f(1, 28) = 12.53$ $p < 0.01$], and cerebellum [$t(28) = 6.29$ $p < 0.05$]

Given the results discussed in sections 3.3.1 and 3.3.2., the main effect of cue type (selection versus non-selection) was, as expected, significant in multiple WM-related ROIs during both the cue and delay phases of the WM task. During the cue phase, increased activity during selection trials (Select-face and Select-scene) compared to non-selection trials was significant in the left MFG [$f(2, 27) = 3.73$ $p < 0.05$], right precuneus [$f(2, 27) = 3.43$ $p < 0.05$] and trended towards significance in the SMA [$f(2, 27) = 3.04$ $p = 0.06$]. During the post-cue delay period, a significant cue effect was observed in the right ACC [$f(2, 27) = 4.41$ $p < 0.05$], SMA [$f(2, 27) = 6.43$ $p < 0.01$], basal ganglia [$f(2, 27) = 5.19$ $p < 0.01$], left [$f(2, 27) = 3.83$ $p < 0.05$] and right [$f(2, 27) = 3.58$ $p < 0.05$] IPS, the left SPL [$f(2, 27) = 10.071$ $p < 0.0001$], the cuneus [$f(2, 27) = 4.40$ $p < 0.05$], precuneus [$f(2, 27) = 3.70$ $p < 0.05$], and cerebellum [$f(2, 27) = 12.44$ $p < 0.001$]. A group by cue-type interaction also trended towards significance in the left cuneus [$f(2, 27) = 3.01$ $p = 0.06$], which showed greater selection-related activity (both Select-face and Select-scene) in MDD subjects than controls, and the SMA [$f(1, 28) = 2.80$ $p < 0.09$], which showed the opposite pattern.

3.3.5 Correlation between Selection-Related Activity and Behavior

For healthy controls, overall response accuracy (Table 3.24) and OSPAN scores (Table 3.25) positively correlated with activity in the left SPL, right parahippocampal gyrus, and left and right anterior cingulate during the cue phase in overall selection>non-selection comparisons(see Figure 3.05a). In the MDD group, activity in the cuneus positively correlated with both measures (Table 3.26, Table 3.27).

In addition, scores on the IDS, RRS, and STAI (both the state and trait questionnaires) also significantly correlated with overlapping clusters in the cuneus for MDD, but not the healthy control, group subjects (3.06a). However, because these scores were significantly correlated with one another (Figure 3.06b), these results cannot be said to be independent.

3.4 Chapter Discussion

The results of analyses outlined in this chapter supported both our hypothesis that major depressive disorder (MDD) would be associated with decreased activity in the congregation of brain regions that support working memory (WM) processing and our alternative hypothesis that MDD would be associated with increased activity in brain regions associated with cognitive

processing. Though MDD group subjects showed overall decreases in WM-related brain regions during multiple phases of our WM selection task, we observed significantly increased selection-related activity in medial parietal and occipital regions (most notably the cuneus) in MDD group subjects compared to controls. Overall, these analyses lend further support to our previous finding that significant deficits in behavioral measures of WM do not necessarily indicate an absence of disruption in the distributed network of brain regions underlying WM selection and maintenance.

While previous studies examining MDD-related dysfunction in WM processing have focused on a limited number of brain regions, especially the ventromedial (vmPFC) and dorsolateral (dlPFC) prefrontal cortices (for review, Clark et al., 2009; Thomas & Elliot, 2009), the analyses outlined in this chapter indicate that the disease significantly disrupts activity in a number of brain regions involved in the control of information in WM. While healthy control subjects demonstrated selection-related activity in regions commonly associated with the control of WM, including the ventrolateral PFC (for review, Badre & Wagner, 2007) and the posterior parietal cortex (for review, Jonides et al., 2008; Miller & Cohen, 2001; Postle, 2006; Ranganath & D'Esposito, 2005), subjects in the MDD group primarily showed selection-related activity in the medial parietal and occipital lobes (most notably the cuneus). Because this altered pattern of selection-related activity was observed in the absence of behavioral deficits, it is somewhat unclear if this altered pattern represented a disruption caused by MDD, a compensatory engagement of other cognitive processes enabling subjects with MDD to perform at the same level as control subjects, or some combination of both.

3.4.1 Working Memory Functioning in Individuals with MDD

The analyses discussed in this chapter point to dysfunction in multiple brain regions (and groups of brain regions) that have, as of this writing, not received significant attention for their role in instantiating the WM deficits observed in subjects with MDD. As previously noted, owing to its limited capacity, optimal WM performance relies on the efficient control of information through working memory (Hasher & Zacks, 1988; Hasher et al., 1999; Cowan, 2010). Work in healthy subjects has indicated that such control is supported by activity in multiple brain regions, including the ventrolateral PFC (Badre & Wagner, 2007; Brass & von Cramon, 2002; Murray et al., 2000; Passingham, et al., 2000; Toni et al., 2001) and the basal ganglia (McNab & Klingberg, 2007). Our observation of attenuated vlPFC activity both prior to the onset of the selection cue and during the post-cue delay period in the MDD group indicates that the disease may be related to difficulties in the efficient control of information both before and after the presentation of selection cues.

Similar to the results discussed in chapter two, activity related to the selection of both faces and scenes was disrupted in the MDD group compared to controls, adding additional evidence to our earlier finding that the disease may significantly affect the processing of information more generally than implied by the results of studies examining difficulties related to the processing of just face stimuli.

3.4.2 The Selection of Faces and Scenes in MDD

Similar to the results described in chapter two, the selection of both face and scene stimuli appeared to be disrupted in MDD group subjects compared to controls. Supporting the assertions outlined in section 2.4.3, the selection of face stimuli appeared to be particularly disrupted in MDD group subjects during the cue phase- with significant clusters in select-face >

non-selection and non-selection > select-face comparisons yielding significant clusters in the healthy control group only. However, because activity related to the selection of scene stimuli and selection overall (Select-face + Select-scene) were also disrupted in MDD group subjects compared to control, the analyses discussed in this chapter support our previous finding that MDD may be related to a disruption in information processing than indicated in previous studies investigating deficits specific to face processing.

The results of both our between and within groups analyses of control and MDD group subjects revealed that though the control group showed significant selection-related activity mainly in frontal and parietal regions, the MDD group mainly showed significant clusters in temporal/occipital regions, including the cuneus. Thus, while it appears that face stimuli may lead to a heightened level of disruption compared to other visual stimuli categories, such disruption is by no means unique to just faces. Indeed, evidence from our *a priori* ROI analysis revealed that MDD-related disruptions mostly manifested as an overall decrease in activity in WM-related brain regions, regardless of cue (or probe) condition. Because these disruptions were observed in the absence of any significant deficits observable at the behavioral level, these results suggest that MDD-group subjects (or at least those exhibiting comparable performance as controls) may be making use of a putative compensatory action in a different group of brain regions.

3.4.3 Compensatory Action: A Role for Medial Parietal and Occipital Regions?

An increasingly large body of research has implicated a network of brain regions, including the IPS, SPL, and multiple clusters within the dorsal PFC in maintaining endogenous (or preparatory) signals based on current task goals or memories (e.g. Astafiev et al., 2003; Corbetta et al., 2000; Pessoa et al., 2002). In contrast, a related- though functionally and anatomically distinct- network, which includes the cuneus, has been implicated in the detection of behaviorally relevant stimuli in the current environment (e.g. Corbetta et al., 2000; Downer et al., 2000). Thus, while one network has been hypothesized to support "top-down" or goal driven attention- which drives preparatory behavior, the other is hypothesized to support stimulus-driven or "bottom-up" attention- which drives more reactive behavior. With this in mind, the increased activity observed in the cuneus of MDD group subjects, especially those showing a high level of behavioral performance, during the cue phase of the WM selection task may represent a compensatory action- a reactive allocation of attention in response to the behaviorally relevant stimuli that is the WM-task cue.

This notion, that the increase in cuneus activity in MDD group subjects represents some form of compensatory activity, is supported by several studies indicating a link between cognitive deficits and structural changes in this region. Work with schizophrenic subjects has demonstrated a significant correlation between reductions in myelination in the cuneus (as measured by fractional anisotrophy) and impairments in processing speed (Palaniyappan et al., In Press). Though we can find no study that has directly examined the role of the cuneus in cognitive processing in subjects with MDD, work with subjects with bipolar disorder type 1 has indicated a positive correlation between gray matter volume in the cuneus and performance on an inhibitory control task (Haldane et al., 2008). Though these results are intriguing, it should be noted that the body of studies examining the link between the cuneus and psychopathology-related cognitive deficits is quite small, with neither study specifically examining MDD. Therefore, until further research is conducted, the notion that activity in the cuneus may represent compensatory action must remain an intriguing possibility rather than a formal

hypothesis. The significant correlation between task performance and cuneus activity discussed in the next section could be interpreted as support, but maybe not.

3.4.4 Correlations between cuneus activity, task performance, and disease severity

Further evidence that the increased selection-related activity in the cuneus of MDD group subjects represented a form of compensatory action comes from the results of correlation analyses investigating clusters of brain activity that correlate with measures of WM task performance and disease severity. While behavioral measurements of WM generally correlated with activations in prefrontal regions (i.e. regions typically associated with WM process) in control group subjects, similar correlations were generally only observed in the cuneus of MDD group subjects. The positive correlation between activity in this region and nearly all measures of MDD symptology indicates that compensatory activity in this region becomes more necessary as disease severity increases.

Because MDD-group subjects did not perform significantly worse than controls on the WM selection task, it appears that the compensatory activity in the cuneus is, at least in the context of our task and the generally mild disease severity exhibited by the MDD group subjects, possibly enough to make up for the concurrent decreases in frontal-parietal regions of interest. However, because there is only a small amount of research examining this region in this context, future research is necessary to address exactly what role the cuneus may be playing.

3.4.5 Future Directions

Thought the present set of analyses provides some intriguing insights into how MDD affects selective information processing, future research is required to answer several questions left open by our use of complex visual stimuli and a task designed to explore only brain activity associated with "top-down" (and not "bottom-up") cognitive processing.

Complex visual stimuli were used in the present study in order to examine MDD-related disruptions both in visual association regions associated that show selective responses to different categories of visual stimuli (namely faces and scenes) and in WM-related brain regions uncovered by a previous study in our lab (Oh & Leung, 2010). While the use of such stimuli enabled us to answer some questions regarding the uniqueness of MDD related deficits in face-processing, the use of such complex stimuli has not enabled us to fully explore the group differences in attentional deployment inferred from the results described in this chapter.

In a study designed to explore common neural activity associated with the orientation of attention to internal and external stimuli held in working memory, Griffin and Nobre (2003) used a paradigm featuring cues presented both before and after the onset of study stimuli. Studies using this task have demonstrated both common and differential activity in the prefrontal and parietal cortices associated with stimulus and goal driven attention (for review, Gazzaley & Nobre, 2012; Lepsien & Nobre, 2006). A future study, using a similar paradigm, would enable us to disentangle whether MDD group subjects show an overall increase in brain activity associated with stimulus-driven attention, or if such increases represent compensatory action evident only during goal-driven behavior.

Because the selection of face stimuli appeared to be particularly disrupted in MDD group subjects, future studies are also necessarily to explore how other variables, including the social and emotional content of experimental stimuli affects activity in the WM and attention related brain regions investigated in this chapter. Also, owing again to our focus on top-down cognitive processing, we were unable to investigate how study parameters have affected our results. To

investigate the time-course of WM related dysfunction and potentially bottom-up attentional compensation, future studies, using variable presentation times, will be necessary. Because the task used in the present study was relatively easy, we were unable to test the limits of the possible compensatory action observed in the cuneus. Future studies, in which subjects are presented with more difficult selection cues or asked to remember a greater number of stimuli, are necessarily to determine trajectory of compensatory activations as task difficulty increases.

Finally, as discussed in the general introduction, MDD is associated with a large number of significant structural changes to the brain. Because of the close link between the BOLD signal and brain morphology (see Logothetis & Wendell, 2004), MDD-related changes in the volume, cellular make-up, and neurochemistry of the brain can complicate the interpretation of functional imaging studies. Overcoming this complication will require future studies to utilize one of two strategies. First, future studies should employ new programs and methods to detect and overcome difficulties such as changed hemodynamic response or altered signal to noise ratio caused by MDD-related differences in brain morphology. Similar to how ArtRepair was applied in the present study to examine and overcome problems related to subject motion; the body of research dealing with the neural basis of cognition in the aging brain has already begun to tools that can be applied for this purpose (see Samanez-Larkin & D'Esposito, 2008). Second, future studies should take advantage of any opportunity to collect structural alongside functional data. Though it could not be completed in time for this manuscript, the structural images collected as part of the present study could be applied to voxel-based morphology (VBM). Similarly, arterial spin labeling (ASL) data was collected for several subjects. When possible, structural data should be presented alongside functional in order to disentangle how MDD-related changes in brain morphology may inform the results of functional imaging studies.

Chapter 4
General Discussion: Symptom and neuroscience-based definitions of major depressive disorder

4.1 General Discussion

The analyses described in this manuscript were designed to address two of the major open questions regarding information processing in MDD. The analyses described in chapter two were designed to examine how MDD affects selective information processing in extrastriatal brain regions that selectively respond to face and scene stimuli. Owing to their social and emotional content, many researchers have posited that the processing of faces is uniquely disrupted in MDD (Stuhrmann et al., 2011). For this reason, we hypothesized that MDD would selectively disrupt activity in face-processing regions including the fusiform and occipital faces areas. Contrary to these hypotheses, MDD-related disruptions were primarily observed in regions commonly associated with the selective processing of scenes- namely the parahippocampal gyrus and retrosplenial cortex. These results not only indicate that face-processing deficits in MDD are not necessarily unique, and that MDD affects processing in regions beyond just the PFC and amygdala, but also that MDD may relate to disrupted activity in a posterior medial system that has been associated with memory retrieval and contextual processing (Squire et al., 2004; Ranganath & Ritchey, 2012). Extending these findings, the analyses described in chapter three demonstrated that MDD significantly affects activation in the network of brain regions supporting working memory selection and maintenance. While previous studies have implicated PFC hyperactivity in subjects with MDD completing working memory tasks at the same level as matched controls (Matsuo et al., 2010), our exploratory whole brain analyses indicated these analyses demonstrated that MDD is associated with decreased activity in brain regions associated with "top-down" cognitive control with a corresponding, potentially compensatory, increase in regions supporting "bottom-up" attention. Together these analyses demonstrate that MDD affects processing in brain regions beyond those identified in studies that have often focused on a small number of regions including the prefrontal cortex and amygdala.

The constellation of symptoms currently defined as major depressive disorder is associated with disruptions in the brain at every available level of analysis; including alterations evident at the cellular level in post-mortem tissue, significant differences in the volume of individual brain regions, significantly altered patterns in task-based BOLD activity, and differences in functional connectivity between brain regions. That information processing should be affected given such widespread changes is hardly surprising. Perhaps more surprising is that, despite these changes, subjects with MDD are often able to complete laboratory tasks on a level not significantly different than healthy controls.

Research examining the aging brain may shed some light on what the results of this and other studies demonstrating disruptions in the WM-related brain regions in the absence of significant behavioral deficits. Similar to what was observed in MDD-group subjects in the present study, aged subjects generally demonstrate decreased activity in brain regions supporting high-order cognitive processes as well as a dampening of activity in brain regions that selectively respond under different task conditions (for review, Bishop et al., 2010; Park & Reuter-Lorenz, 2009). Also similar to was observed in MDD-group subjects in the present study, potentially compensatory brain activity has often been observed in studies in which aged subjects perform on the same level as younger controls (e.g. Cabeza et al., 1997; 2002; Grady et al., 1999). While

there are very likely significant differences between disrupted activity caused by MDD and altered activity observed during normal aging, research examining age-related alterations in brain activity and the trajectory of potentially compensatory activity in aged subjects may support the results of the present study and indicate the direction of future research.

In studies of aged subjects, the presence of compensatory activity in the prefrontal cortex has been linked to disrupted activity in the parahippocampal gyri (Gutchess et al., 2005; Johnson et al., 2004; Park et al., 2004)- the same region shown to be disrupted in the present study in MDD-group subjects. In a study by Cabeza et al. (2004), decreased hippocampal and parahippocampal activity was observed across a range of attention, working memory, and long-term memory tasks, implying that this disruption in relatively global. Most relevant to the analyses discussed in chapter two of this thesis, aged subjects have shown markedly less selectivity in the fusiform face area (FFA) and parahippocampal place area (PPA) compared to controls (Park et al., 2004; Payer et al., 2006)- also similar to what was observed in MDD group subjects in the present study.

Compensatory activity, in terms of increasing recruitment of bilateral clusters within the PFC, has been observed in young adults as task complexity increases (Banich, 1998) and when young adults are deprived of sleep (Drummand et al., 2004), indicating that compensatory activity observed in aged (and potentially MDD group) subjects may be an extended version of a transient state that occurs in healthy subjects when task demands are high. In presence of compensatory activity has been correlated with increasing shrinkage of hippocampal regions of aged subjects (Persson et al., 2006), which indicates that MDD-related deficits may be due to disruptions in these and other regions as well. Though regions such as the PFC and amygdala are logical targets for studies investigated MDD-related cognitive deficits, the complexity of disease symptoms, the association of the disease with widespread dysfunction in a multitude of brain regions affecting many mental and physical processes, and the presence of putative compensatory action in, at least some, subjects with MDD indicates that the study of the neural basis of MDD requires a much broader study of the relationship between MDD-related disruptions in brain activity and symptoms and deficits observed at the behavioral level.

4.2 Future directions: Defining Major Depression

As of this writing, two major developments are underway that may significantly alter how mental disorders such as MDD are studied in the laboratory. First, the BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative, recently unveiled by the National Institutes of Health, has been established to help researchers to develop new tools for examining and treating brain-based disorders and form a dynamic picture of information processing in the brain at every level of analysis (The White House, 2013). Though still in its earliest phases, the BRAIN initiative includes ambitious plans to completely map the human brain using techniques drawn from neuroscience, brain imaging, engineering, and bioinformatics (Alvisatos et al., 2012; 2013). A project of this scale has implications not just for the study of MDD through (potentially) allowing researchers to investigate MDD-related disruptions in brain activity beyond discrete regions of interest including the prefrontal cortex and amygdala, but also for tremendously advancing research into how activity in the brain relates to behavior under normal conditions. Second, the National Institute of Mental Health (NIMH) has recently announced a long-term plan to develop new diagnostic criteria and treatments for mental disorders based on genetic, physiological, and cognitive data rather than behavioral symptoms

alone (Insel, 2013). In NIMH's new framework, called Research Domain Criteria (RDoC), mental disorders such as MDD will be defined not just by clusters of symptoms, but also by biomarkers drawn from empirical studies.

In many ways, both developments are in line with the goals of the present study. Existing gaps in the literature describing MDD-related cognitive deficits, at least in part, appear to be due to an understandable focus on the most obviously debilitating symptoms of the disease as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (see commentary by Holtzheimer & Mayberg, 2011). However, the focus on disruptions related to relatively narrow aspects of cognition (i.e. the processing of emotional faces) and a limited number of corresponding brain regions (i.e. the prefrontal cortex and amygdala) has precluded the examination of broader cognitive deficits and disrupted activity in loci with less obvious ties to the major diagnostic criteria for MDD. While the present study demonstrates that MDD is associated with disrupted activity in multiple brain regions that have not been the central target of previous research, it should not be interpreted as evidence that future research should focus completely on biological markers of the disease.

Currently, aside from studies examining face-processing deficits, only a relatively small number of studies have examined neural and behavioral disruptions associated with the individual symptoms of MDD. Even in the body of studies discussed in this manuscript concerning disruptions in cognition, many studies appear have examined overall disruptions in cognition rather than disruptions related to specific cognitive processes. The results of the present study- demonstrating that MDD significantly affects activity in regions associated with selective information processing and stimulus-driven attention control- indicate that the disease affects a broad swath of neural activity and cognitive processes. However, far more additional research is required before diagnostic criteria for MDD can be derived on reliable biomarkers. For example, though there is some evidence that MDD significantly affects visual processing at levels even lower than observed in the present study (e.g. Desseilles et al., 2009; 2011), such disruptions have yet to be thoroughly investigated. In addition, MDD-related deficits in the processing of information outside the visual modality, or of information that does not necessarily have strong emotional content, have been the target a relatively small amount of empirical research (see Takei et al., 2009; Walter et al., 2007). Beyond further research into disruptions during the acute phase of the disease, transitioning to biomarker-based diagnostic criteria would also require a much larger body of research examining disruptions in subjects with remitted MDD and subjects at risk for depression. While several lines of research have begun to identify neural and behavioral deficits in subjects at risk for the disease (e.g. Kujawa et al., 2011; Mannie et al., 2008) and in remitted subjects (e.g. Kerestes et al., 2011; Paelecke-Habermann et al., 2005), there are at present no reliable biomarkers for MDD prior to, during, or following a depressive episode (Hammar & Ardal, 2009).

Given the relatively narrow focus and general heterogeneity of results in the current body of research, the major gaps that need to be addressed via empirical study, and the lack of any reliable biomarker for MDD, any transition to biology-informed diagnostic criteria would be premature. Though, conditions like ischemic heart disease, lymphoma, and acquired immunodeficiency syndrome (AIDS) can be detected by relatively objective laboratory measures, rather than clusters of clinical symptoms (Insel, 2013), the same cannot yet be said for the majority of disorders currently defined by the DSM.

While using the DSM (or really, any other standardized criteria) to define a mental disorder can be problematic, owing to the supreme difficulty in categorizing concepts as

amorphous as mental disorders (see commentary by Frances & Widiger, 2012), DSM-based definitions have the advantage of being easily operationalized in a manner that allows for researchers to group similar afflicted patients and gather empirical data. However, while DSM criteria provide reliable operational definitions, their validity is limited by a lack of etiological and psychophysiological information (Hyman, 2007). Furthermore, likely because of the paucity of other available definitions, DSM criteria are often reified. Criteria designed to act as (generally) reliable heuristics in communication about, and study of, mental disorders are instead interpreted as encompassing natural entities- existing independently of rating criteria or theoretical constructs (Kendell & Jablensky, 2003; Hyman, 2010). Because of this, while DSM criteria have, perhaps by necessity, been used to operationalize mental disorders for research purposes- as they were in the present study- the reification of DSM criteria has likely also limited the scope of experimental research.

Limitations in current neuroscientific accounts of mental disorders along with difficulties inherent in using DSM definitions have resulted in the epistemological stalemate that underlies the current knowledge gaps in research examining the neural basis of MDD-related cognitive deficits. Adherence to studying major DSM criteria for the disease, including depressed mood and feelings of guilt and worry, has resulted in a relatively large number of studies examining the neural basis emotion-regulation and rumination. This, in turn, has led to a focus on brain regions believed to be heavily involved in these processes, especially the amygdala and prefrontal cortex. This has left MDD-related deficits in specific cognitive processes- especially as reflected by disruptions within the broad network of brain regions supporting working memory- relatively unclear until the present study. In turn, though the present study provides some intriguing insight into how MDD affects selective information processing in MDD, such findings are not, on their own, to jettison DSM-based definitions. Much additional research is required to further delineate the breadth and depth of the disruptions described in the two sets of analysis described in this manuscript and even more research would be required to determine if such disruptions are unique enough to MDD to ask as reliable biomarkers.

Rather than relying strictly on neuroscience or DSM-based criteria, the progress of research into the neural basis of mental disorders (not just MDD, but especially for disorders as heterogeneous as MDD) requires a gradual evolution of both. Current brain-based models of disorders like MDD are insufficient to replace symptom-based criteria like those used in the DSM. However, DSM criteria should also not limit the scope of research into the neuroscientific basis of mental disorders. Instead, the two perspectives should inform each other. Definitions of mental disorders should be informed by neuroscience research and, at least until valid and reliable biomarkers can be found- symptom-based based definitions should inform, but not restrict, research examining the neural basis of mental disorders.

Works Cited

Abercrombie, H. C., Schaefer, S. M., Larson, C. L., Ward, R. T., Holden, J. E., Turski, P. A., Perlman, S. B., & Davidson, R. J. (1996). Medial prefrontal and amygdalar glucose metabolism in depressed and control subjects: An FDG-PET study. *Psychophysiology, 33*, S17.

Abercrombie, H. C., Schaefer, S. M., Larson, C. L., Oakes, T. R., Lindgren, K. a, Holden, J. E., Perlman, S. B., et al. (1998). Metabolic rate in the right amygdala predicts negative affect in depressed patients. *Neuroreport*, *9*(14), 3301–3307.

Alderson, R. M., Rapport, M. D., & Kofler, M. J. (2007). Attention-deficit/hyperactivity disorder and behavioral inhibition: a meta-analytic review of the stop-signal paradigm. *Journal of abnormal child psychology*, *35*(5), 745–758.

Alivisatos, a P., Chun, M., Church, G. M., Greenspan, R. J., Roukes, M. L., & Yuste, R. (2012). The brain activity map project and the challenge of functional connectomics. *Neuron*, *74*(6), 970–974.

Alivisatos, A. P., Chun, M., Church, G. M., Deisseroth, K., Donaghue, J. P., Greenspan, R. J., McEuen, P. L., et al. (2013). The Brain Activity Map. *Science*, *339*, 9–10.

Amaral, D. G. & Price, J. L. (1984). Amygdalo-cortical projections in the monkey (Macaca fascicularis). *Journal of comparative neurology*, 230, 465–496.

Aminoff, E., Gronau, N., & Bar, M. (2007). The parahippocampal cortex mediates spatial and nonspatial associations. *Cerebral cortex*, *17*(7), 1493–1503.

Aminoff, E, Schacter, D. L., & Bar, M. (2008). The cortical underpinnings of context-based memory distortion. *Journal of cognitive neuroscience*, *20*(12), 2226–2237.

Aminoff, E., Kveraga, K., Bar, M. (In Press). The role of the parahippocampal gyrus in cognition. *Trends in cognitive science.*

Anand, A., Li, Y., Wang, Y., Wu, J., Gao, S., Bukhari, L., Mathews, V. P., et al. (2005). Antidepressant effect on connectivity of the mood-regulating circuit: an FMRI study. *Neuropsychopharmacology*, *30*(7), 1334–1344.

Andrews, P. W., Kornstein, S. G., Halberstadt, L. J., Gardner, C. O., & Neale, M. C. (2011). Blue again: perturbational effects of antidepressants suggest monoaminergic homeostasis in major depression. *Frontiers in psychology*, 159(*2*).

Astafiev, S. V, Shulman, G. L., Stanley, C. M., Snyder, A. Z., Van Essen, D. C., & Corbetta, M. (2003). Functional organization of human intraparietal and frontal cortex for attending, looking, and pointing. *The Journal of neuroscience*, *23*(11), 4689–4699.

Aston, C., Jiang, L., & Sokolov, B. P. (2005). Transcriptional profiling reveals evidence for signaling and oligodendroglial abnormalities in the temporal cortex from patients with major depressive disorder. *Molecular psychiatry*, *10*(3), 309–322.

Austin, M. P., Mitchell, P., & Goodwin, G. M. (2001). Cognitive deficits in depression: possible implications for functional neuropathology. *The British journal of psychiatry : the journal of mental science*, *178*, 200–206.

Baddeley, A. D. (1986). Working Memory. Oxford: Clarendon Press.

Baddeley, A. D. (2003). Working memory: looking back and looking forward. *Nature reviews: Neuroscience*, *4*(10), 829–839.

Baddeley, A.D. & Hitch, G. J. (1974) Working memory. In: Bower, G. (eds) Recent advances in learning and motivation. London: Academic Press

Badre, D., & Wagner, A. D. (2005). Frontal lobe mechanisms that resolve proactive interference. *Cerebral cortex*, *15*(12), 2003–2012.

Badre, D., & Wagner, A. D. (2007). Left ventrolateral prefrontal cortex and the cognitive control of memory. *Neuropsychologia*, *45*(13), 2883–901.

Badre, D., Poldrack, R. a, Paré-Blagoev, E. J., Insler, R. Z., & Wagner, A. D. (2005). Dissociable controlled retrieval and generalized selection mechanisms in ventrolateral prefrontal cortex. *Neuron*, *47*(6), 907–918.

Banasr, M., & Duman, R. (2008). Glial loss in the prefrontal cortex is sufficient to induce depressive-like behaviors. *Biological psychiatry*, *64*(10), 863–870.

Banich, M. (1998). Integration of information between the cerebral hemispheres. *Current directions in psychological science*, *7*(1), 111–116.

Bar, M. (2009). A cognitive neuroscience hypothesis of mood and depression. *Trends in cognitive sciences*, *13*(11), 456–463.

Bar, M., Aminoff, E., & Ishai, A. (2008). Famous faces activate contextual associations in the parahippocampal cortex. *Cerebral cortex*, *18*(6), 1233–1238.

Bar, M., Aminoff, E., & Schacter, D. L. (2008). Scenes unseen: the parahippocampal cortex intrinsically subserves contextual associations, not scenes or places per se. *The Journal of neuroscience*, *28*(34), 8539–8544.
Barbas, H. (2000). Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices. *Brain research bulletin*, *52*(5), 319–330.
Barbas, H., & De Olmos, J. (1990). Projections from the amygdala to basoventral and mediodorsal prefrontal regions in the rhesus monkey. *The Journal of comparative neurology*, *300*(4), 549–571.
Barbas, H., Pandya, D. N (1989). Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. *Journal of comparative neurology, 286, 353-375*
Barbas, H., Ghashghaei, H., Dombrowski, S. M., Rempel-Clower, N. L. (1999). Medial prefrontal cortices are unified by common connections with superior temporal cortices and distinguished by input from memory-related areas in the rhesus monkey. *Journal of comparative neurology*, 410, 343–367,
Barch, D. M., Sheline, Y. I., Csernansky, J. G., & Snyder, A. Z. (2003). Working memory and prefrontal cortex dysfunction: specificity to schizophrenia compared with major depression. *Biological psychiatry*, *53*(5), 376-384.
Baxter, L. R., Schwartz, J. M., Phelps, M. E., Mazziota, J. C., Guze, B. H., Selin, C. E., Gerner, R. H., Sumida, R. M., (1989). Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Archive of General Psychiatry, 46,* 243–250.
Beck, A. T. (1967). *Depression: Clinical, experimental, and theoretical aspects*. New York: Harper & Row.
Beck, A. T. (2008). The evolution of the cognitive model of depression and its neurobiological correlates. *The American journal of psychiatry*, *165*(8), 969–977.
Belmaker, R. H., & Agam, G. (2008). Major depressive disorder. *The New England journal of medicine*, *358*(1), 55–68.
Berman, M. G., Nee, D. E., Casement, M., Kim, H. S., Deldin, P., Kross, E., Gonzalez, R., et al. (2011). Neural and behavioral effects of interference resolution in depression and rumination. *Cognitive, affective & behavioral neuroscience*, *11*, 85–96.
Bishop, N. A, Lu, T., & Yankner, B. A. (2010). Neural mechanisms of ageing and cognitive decline. *Nature*, *464*(7288), 529–535.
Bistricky, S. L., Ingram, R. E., & Atchley, R. A. (2011). Facial affect processing and depression susceptibility: Cognitive biases and cognitive neuroscience. *Psychological bulletin*, *137*(6), 998-1028.
Biver, F., Goldman, S., Delvenne, V., Luxen, A., De Maertelaer, V., Hubain, P. Mendlewicz, J., & Lotstra, F. (1994). Frontal and parietal metabolic disturbances in unipolar depression, *Biological Psychiatry*, 36, 381–388.
Bjorklund, D. F., & Harnishfeger, K. K. (1990). The resources construct in cognitive development: Diverse sources of evidence and a theory of inefficient inhibition. *Developmental review*, *10*(1), 48-71.
Bocanegra, B. R., & Zeelenberg, R. (2009). Emotion improves and impairs early vision. *Psychological Science*, *20*(6), 707-713.
Bocanegra, B. R., & Zeelenberg, R. (2011). Emotional cues enhance the attentional effects on spatial and temporal resolution. *Psychonomic bulletin & review*, *18*(6), 1071–1076.
Bonne, O., Krausz, Y., Shapira, B., Bocher, M., Karger, H., Gorfine, M., Chisin, R. & Lerer, B. (1996). Increased cerebral blood flow in depressed patients responding to electroconvulsive therapy. *Journal of Nuclear Medicine, 37,* 1075–1080.
Bora, E., Fornito, A., Pantelis, C., & Yücel, M. (2012). Gray matter abnormalities in Major Depressive Disorder: a meta-analysis of voxel based morphometry studies. *Journal of affective disorders*, *138*(1-2), 9–18.
Bora, E., Harrison, B. J., Yücel, M., & Pantelis, C. (2012b). Cognitive impairment in euthymic major depressive disorder: a meta-analysis. *Psychological medicine*, (October 2012), 1–10.
Bower, G. H. (1981). Mood and memory. *The American psychologist*, *36*(2), 129–48.
Bradley, B., Mogg, K., & Lee, S. (1997). Attentional biases for negative information in induced and naturally occurring dysphoria. B*ehaviour research and therapy*, *35*(10), 911--927
Bremner, J., & Narayan, M. (2000). Hippocampal Volume Reduction in Major Depression. *American Journal of Psychiatry* 157(1), 115–117.
Brett, M., Anton, J. L., Valabregue, R., & Poline, J. B. (2002). Region of interest analysis using an SPM toolbox [abstract] Presented at the 8th International Conference on Functional Mapping of the Human Brain, June 2-6, 2002, Sendai, Japan.
Brown, M. W., & Aggleton, J. P. (2001). Recognition memory: What are the roles of the perirhinal cortex and hippocampus? *Nature Reviews Neuroscience*, *2*(January), 51–61.

Brozoski, T. J., Brown, R. M., Rosvold, H. E., & Goldman, P. S. (1979). Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. *Science*, *205*(4409), 929-932.
Bowley, M. P., Drevets, W. C., Öngür, D., & Price, J. L. (2002). Low glial numbers in the amygdala in major depressive disorder. *Biological psychiatry*, *52*(5), 404-412.
Brass, M., & Von Cramon, D. Y. (2002). The role of the frontal cortex in task preparation. *Cerebral cortex*, *12*(9), 908–914.
Bubl, E., Kern, E., Ebert, D., Bach, M., & Tebartz van Elst, L. (2010). Seeing gray when feeling blue? Depression can be measured in the eye of the diseased. *Biological psychiatry*, *68*(2), 205–208.
Bubl, E., Ebert, D., Kern, E., Van Elst, L. T., & Bach, M. (2012). Effect of anti-depressive therapy on retinal contrast processing in depressive disorder. *The British journal of psychiatry*, *201*(2), 151-158.
Burgess, N., Maguire, E. a, & O'Keefe, J. (2002). The human hippocampus and spatial and episodic memory. *Neuron*, *35*(4), 625–641.
Burt, D. B., Zembar, M. J., & Niederehe, G. (1995). Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. *Psychological bulletin*, *117*(2), 285–305.
Cabeza, Roberto, Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging Gracefully: Compensatory Brain Activity in High-Performing Older Adults. *Neuroimage*, *17*(3), 1394–1402.
Cabeza, R, Grady, C. L., Nyberg, L., McIntosh, A. R., Tulving, E., Kapur, S., Jennings, J. M., et al. (1997). Age-related differences in neural activity during memory encoding and retrieval: a positron emission tomography study. *The Journal of neuroscience*, *17*(1), 391–400.
Cabeza, R., Prince, S. E., Daselaar, S. M., Greenberg, D. L., Budde, M., Dolcos, F., LaBar, K. S., et al. (2004). Brain activity during episodic retrieval of autobiographical and laboratory events: an fMRI study using a novel photo paradigm. *Journal of cognitive neuroscience*, *16*(9), 1583–1594.
Cabeza, R., & St Jacques, P. (2007). Functional neuroimaging of autobiographical memory. *Trends in cognitive sciences*, *11*(5), 219–227.
Caetano, S. C., Hatch, J. P., Brambilla, P., Sassi, R. B., Nicoletti, M., Mallinger, A. G., et al. (2004). Anatomical MRI study of hippocampus and amygdala in patients with current and remitted major depression. *Psychiatry research: Neuroimaging*, *132*(2), 141-147.
Carmichael, S. T., & Price, J. L. (1995). Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. *The Journal of comparative neurology*, *363*(4), 615–641.
Carmichael, S. T., & Price, J. L. (1996). Connectional networks within the orbital and medial prefrontal cortex of macaque monkeys. *The Journal of comparative neurology*, *371*(2), 179–207.
Carragher, N., Adamson, G., Bunting, B., & McCann, S. (2009). Subtypes of depression in a nationally representative sample. *Journal of Affective Disorders*, *113*(1), 88-99.
Caseras, X., Garner, M., Bradley, B. P., & Mogg, K. (2007). Biases in visual orienting to negative and positive scenes in dysphoria: An eye movement study. *Journal of abnormal psychology*, *116*(3), 491–497.
Castaneda, A. E., Tuulio-Henriksson, A., Marttunen, M., Suvisaari, J., & Lönnqvist, J. (2008). A review on cognitive impairments in depressive and anxiety disorders with a focus on young adults. *Journal of affective disorders*, *106*(1-2), 1-27.
Cavada, C., & Goldman-Rakic, P. S. (1989). Posterior parietal cortex in rhesus monkey: II. Evidence for segregated corticocortical networks linking sensory and limbic areas with the frontal lobe. *The Journal of comparative neurology*, *287*(4), 422–445.
Cavanna, A. E., & Trimble, M. R. (2006). The precuneus: a review of its functional anatomy and behavioral correlates. *Brain*, *129*(3), 564–583.
Chamberlain, S. R., Blackwell, a D., Fineberg, N. a, Robbins, T. W., & Sahakian, B. J. (2005). The neuropsychology of obsessive compulsive disorder: the importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers. *Neuroscience and biobehavioral reviews*, *29*(3), 399–419.
Cheng, J. D., & de Vellis, J. (2000). Oligodendrocytes as glucocorticoids target cells: functional analysis of the glycerol phosphate dehydrogenase gene. *Journal of neuroscience research*, *59*(3), 436-445.
Chong, S. C., Jo, S., Park, K. M., Joo, E. Y., Lee, M.-J., Hong, S. C., & Hong, S. B. (2013). Interaction between the electrical stimulation of a face-selective area and the perception of face stimuli. *Neuroimage*, *77*, 70–76.
Chumbley, J. R., & Friston, K. J. (2009). False discovery rate revisited: FDR and topological inference using Gaussian random fields. *Neuroimage*, *44*(1), 62–70.
Clark, L., Chamberlain, S. R., & Sahakian, B. J. (2009). Neurocognitive mechanisms in depression: implications for treatment. *Annual review of neuroscience*, *32*, 57–74.
Cools, R., & D'Esposito, M. (2011). Inverted-U shaped dopamine actions on human working memory and cognitive control. *Biological psychiatry*, *69*(12), 113-125

Corbetta, M., Kincade, J. M., Ollinger, J. M., McAvoy, M. P., & Shulman, G. L. (2000). Voluntary orienting is dissociated from target detection in human posterior parietal cortex. *Nature neuroscience*, *3*(3), 292–297.

Costafreda, S. G., McCann, P., Saker, P., Cole, J. H., Cohen-Woods, S., Farmer, A. E., et al. (In Press). Modulation of amygdala response and connectivity in depression by serotonin transporter polymorphism and diagnosis. *Journal of affective disorders*.

Cotter, D, Mackay, D., Landau, S., Kerwin, R., & Everall, I. (2001). Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. *Archives of general psychiatry*, *58*(6), 545–553.

Cotter, David, Mackay, D., Chana, G., Beasley, C., Landau, S., & Everall, I. P. (2002). Reduced neuronal size and glial cell density in area 9 of the dorsolateral prefrontal cortex in subjects with major depressive disorder. *Cerebral cortex*, *12*(4), 386–394.

Cowan, N. (1988). Evolving conceptions of memory storage, selective attention, and their mutual constraints with the human information processing system. *Psychological bulletin*, *104(2), 163-191.*

Cowan, N. (1999). An embedded-process model of working memory. In A. Miyake & P. Shah (eds). *Models of working memory: Mechanisms of active maintenance and executive control.* Cambridge University Press, New York, NY.

Cowan, N. (2010). The Magical Mystery Four: How is Working Memory Capacity Limited, and Why? *Current directions in psychological science*, *19*(1), 51–57.

Dalton, K. M., Nacewicz, B. M., Johnstone, T., Schaefer, H. S., Gernsbacher, M. A., Goldsmith, H. H., Alexander, A. L., et al. (2005). Gaze fixation and the neural circuitry of face processing in autism. *Nature neuroscience*, *8*(4), 519–526.

Daselaar, S. M., Prince, S. E., Dennis, N. a, Hayes, S. M., Kim, H., & Cabeza, R. (2009). Posterior midline and ventral parietal activity is associated with retrieval success and encoding failure. *Frontiers in human neuroscience*, *3*(13)

Davachi, L., Mitchell, J. P., & Wagner, A. D. (2003). Multiple routes to memory: distinct medial temporal lobe processes build item and source memories. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(4), 2157–2162.

Davidson, R. J., Pizzagalli, D., Nitschke, J. B., & Putnam, K. (2002). Depression: perspectives from affective neuroscience. *Annual review of psychology*, *53*, 545–574.

Davis, R. N., & Nolen-Hoeksema, S. (2000). Cognitive inflexibility among ruminators and nonruminators. *Cognitive Therapy and research*, 24, 699−711.

Desseilles, M., Balteau, E., Sterpenich, V., Dang-Vu, T. T., Darsaud, A., Vandewalle, G., Albouy, G., et al. (2009). Abnormal neural filtering of irrelevant visual information in depression. *The journal of neuroscience*, *29*(5), 1395–1403.

Desseilles, M., Schwartz, S., Dang-Vu, T. T., Sterpenich, V., Ansseau, M., Maquet, P., & Phillips, C. (2011). Depression alters "top-down" visual attention: a dynamic causal modeling comparison between depressed and healthy subjects. *Neuroimage*, *54*(2), 1662–1668

Di Pietro, N. C., & Seamans, J. K. (2011). Dopamine and serotonin interactively modulate prefrontal cortex neurons in vitro. *Biological psychiatry*,*69*(12), 1204-1211.

Diana, R. A, Yonelinas, A. P., & Ranganath, C. (2007). Imaging recollection and familiarity in the medial temporal lobe: a three-component model. *Trends in cognitive sciences*, *11*(9), 379–386.

Diener, C., Kuehner, C., Brusniak, W., Ubl, B., Wessa, M., & Flor, H. (2012). A meta-analysis of neurofunctional imaging studies of emotion and cognition in major depression. *Neuroimage*, *61*(3), 677–685.

Drevets, W. C., Bogers, W., & Raichle, M. E. (2002). Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. *European neuropsychopharmacology*,*12*(6), 527-544.

Drevets, W. C., Price, J. L., & Furey, M. L. (2008). Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain structure & function*, *213*(1-2), 93–118.

Drevets, W. C., & Raichle, M. E. (1992). Neuroanatomical circuits in depression: implications for treatment mechanisms. *Psychopharmacology bulletin*, *28*(3), 261-274.

Drummond, S. P. A, Brown, G. G., Salamat, J. S., & Gillin, J. C. (2004). Increasing task difficulty facilitates the cerebral compensatory response to total sleep deprivation. *Sleep*, *27*(3), 445–451.

Dunlop, B. W., & Nemeroff, C. B. (2007). The role of dopamine in the pathophysiology of depression. *Archives of general psychiatry*, *64*(3), 327–337.

Eizenman, M., Yu, L. H., Grupp, L., Eizenman, E., Ellenbogen, M., Gemar, M., & Levitan, R. D. (2003). A naturalistic visual scanning approach to assess selective attention in major depressive disorder. *Psychiatry research*, *118*(2), 117–128.

Elliott, R., Baker, S. C., Rogers, R. D., O'Leary, D. a., Paykel, E. S., Frith, C. D., Dolan, R. J., et al. (1997). Prefrontal dysfunction in depressed patients performing a complex planning task: a study using positron emission tomography. *Psychological medicine*, *27*(4), 931–942.

Enright, S. J., & Beech, A. R. (1990). Obsessional states: Anxiety disorders or schizotypes? An information processing and personality assessment. *Psychological medicine*, *20*(03), 621-627.

Enright, S. J., & Beech, A. R. (1993). Reduced cognitive inhibition in obsessive-compulsive disorder. *British journal of clinical psychology*, *32*(1), 67-74.

Epstein, R., Harris, a, Stanley, D., & Kanwisher, N. (1999). The parahippocampal place area: recognition, navigation, or encoding? *Neuron*, *23*(1), 115–125. R

Epstein, R., & Kanwisher, N. (1998). A cortical representation of the local visual environment. *Nature*, *392*(6676), 598–601.

Epstein, R. (2008). Parahippocampal and retrosplenial contributions to human spatial navigation. *Trends in cognitive sciences*, *12*(10), 388–396.

Eugène, F., Joormann, J., Cooney, R. E., Atlas, L. Y., & Gotlib, I. H. (2010). Neural correlates of inhibitory deficits in depression. *Psychiatry research*, *181*(1), 30–35.

Fairhall, S. L., & Ishai, A. (2007). Effective connectivity within the distributed cortical network for face perception. *Cerebral cortex*, *17*(10), 2400–2406.

Fales, C. L., Barch, D. M., Rundle, M. M., Mintun, M. a, Snyder, A. Z., Cohen, J. D., Mathews, J., et al. (2008). Altered emotional interference processing in affective and cognitive-control brain circuitry in major depression. *Biological psychiatry*, *63*(4), 377–384.

First M. B. , Spitzer RL, Gibbon M, et al. (1997). *Structure Clinical Interview for DSM-IV Axis I Disorders (SCID-I)*. Arlington (VA): American Psychiatric Publishing.

Fitzgerald, P. B., Oxley, T. J., Laird, A. R., Kulkarni, J., Egan, G. F., & Daskalakis, Z. J. (2006). An analysis of functional neuroimaging studies of dorsolateral prefrontal cortical activity in depression. *Psychiatry research*, *148*(1), 33-45.

Fitzgerald, P. B., Laird, A. R., Maller, J., & Daskalakis, Z. J. (2008). A meta-analytic study of changes in brain activation in depression. *Human brain mapping*, *29*(6), 683–695.

Fitzgerald, P. B., Srithiran, A., Benitez, J., Daskalakis, Z. Z., Oxley, T. J., Kulkarni, J., & Egan, G. F. (2008b). An fMRI study of prefrontal brain activation during multiple tasks in patients with major depressive disorder. *Human brain mapping*, *29*(4), 490–501.

Fox, C. J., Iaria, G., & Barton, J. J. S. (2009). Defining the face processing network: optimization of the functional localizer in fMRI. *Human brain mapping*, *30*(5), 1637–1651.

Frances, A. J., & Widiger, T. (2012). Psychiatric diagnosis: lessons from the DSM-IV past and cautions for the DSM-5 future. *Annual review of clinical psychology*, *8*, 109–130.

Frank, M. J., Loughry, B., & O'Reilly, R. C. (2001). Interactions between frontal cortex and basal ganglia in working memory: a computational model. *Cognitive, affective & behavioral neuroscience*, *1*(2), 137–160.

Freese, J., & Amaral, D. (2005). The Synaptic Organization of Projections from the Amygdala to Visual Cortical Areas TE and V1 in the Macaque Monkey. *Journal of Comparative Neurology*, *496*(5), 655–667.

Friston, K. J., Frith, C. D., Liddle, P. F., & Frackowiak, R. S. (1991). Comparing functional (PET) images: the assessment of significant change. *Journal of cerebral blood flow and metabolism*, *11*(4), 690–699.

Friston, K., Holmes, A., & Poline, J. (1995). Analysis of fMRI time-series revisited. *Neuroimage*, *2*, 45–53.

Friston, K. J., Rotshtein, P., Geng, J. J., Sterzer, P., & Henson, R. N. (2006). A critique of functional localisers. *Neuroimage*, *30*(4), 1077–1087.

Frith, C. D. (1979). Consciousness, information processing and schizophrenia. *The British journal of psychiatry*, *134*(3), 225-235.

Foland-Ross, L. C., Hamilton, J. P., Joormann, J., Berman, M. G., Jonides, J., & Gotlib, I. H. (In Press). The Neural Basis of Difficulties Disengaging From Negative Irrelevant Material in Major Depression. *Psychological science*.

Frodl, T., Meisenzahl, E. M., Zetzsche, T., Höhne, T., Banac, S., Schorr, C., et al. (2004). Hippocampal and amygdala changes in patients with major depressive disorder and healthy controls during a 1-year follow-up. *The Journal of clinical psychiatry*, *65*(4), 492-499.

Fu, C. H. Y., Williams, S. C. R., Cleare, A. J., Brammer, M. J., Walsh, N. D., Kim, J., Andrew, C. M., et al. (2004). Attenuation of the neural response to sad faces in major depression by antidepressant treatment. *Archives of general psychiatry*, *61*(9), 877–889.

Fu, C. H. Y., Williams, S. C. R., Cleare, A. J., Scott, J., Mitterschiffthaler, M. T., Walsh, N. D., Donaldson, C., et al. (2008). Neural responses to sad facial expressions in major depression following cognitive behavioral therapy. *Biological psychiatry*, *64*(6), 505–512.

Funahashi, S., & Bruce, C. J. (1989). Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex Mnemonic Coding of Visual Space in the Monkey's Dorsolateral Prefrontal Cortex. *Journal of neurophysiology*, *61*(2), 331–349.

Funahashi, S, Bruce, C. J., & Goldman-Rakic, P. S. (1993). Dorsolateral prefrontal lesions and oculomotor delayed-response performance: evidence for mnemonic "scotomas". *The Journal of neuroscience*, *13*(4), 1479–1497.

Funahashi, S., Chafee, M. V., & Goldman-Rakic, P. S. (1993b). Prefrontal neuronal activity in rhesus monkeys performing a delayed anti-saccade task. *Nature*, *365*, 753–756.

Furey, M. L., Drevets, W. C., Hoffman, E. M., Frankel, E., Speer, A. M., & Zarate, C. A. (2013). Potential of pretreatment neural activity in the visual cortex during emotional processing to predict treatment response to scopolamine in major depressive disorder. *JAMA Psychiatry*, *70*(3), 280–290.

Furl, N., Coppola, R., Averbeck, B. B., & Weinberger, D. R. (In Press). Cross-frequency power coupling between hierarchically organized face-selective areas. C*erebral cortex*.

Fuster, J. (1973). Unit activity in prefrontal cortex during delayed-response performance: neuronal correlates of transient memory. *Journal of neurophysiology*, *36*(1), 61–78.

Fuster, J. (2013). *The prefrontal cortex*. London: Academic Press.

Friedman, N. P., & Miyake, A. (2004). The relations among inhibition and interference control functions: a latent-variable analysis. *Journal of experimental psychology. General*, *133*(1), 101–135.

Garrett, A., Kelly, R., Gomez, R., Keller, J., Schatzberg, A. F., & Reiss, A. L. (2011). Aberrant brain activation during a working memory task in psychotic major depression. *The American journal of psychiatry*, *168*(2), 173–182.

Gauthier, I., Tarr, M., & Moylan, J. (2000). The fusiform "face area" is part of a network that processes faces at the individual level. *Journal of cognitive neuroscience*, (93), 495–504.

Gazzaley, A., & Nobre, A. (2012). Top-down modulation: Bridging selective attention and working memory. *Trends in cognitive sciences*, *16*(2), 129–135.

Genovese, C. R., Lazar, N. a, & Nichols, T. (2002). Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage*, *15*(4), 870–878.

Giovanello, K. S., & Schacter, D. L. (2011). Reduced Specificity of Hippocampal and Posterior Ventrolateral Prefrontal Activity during Relational Retrieval in Normal Aging. *Journal of Cognitive Neuroscience*, *24*(1), 159–170.

Goeleven, E., De Raedt, R., Baert, S., & Koster, E. H. W. (2006). Deficient inhibition of emotional information in depression. *Journal of affective disorders*, *93*(1-3), 149–157.

Goh, J. O., Suzuki, A., & Park, D. C. (2010). Reduced neural selectivity increases fMRI adaptation with age during face discrimination. *Neuroimage*,*51*(1), 336-344.

Gohier, B., Ferracci, L., Surguladze, S. A., Lawrence, E., El Hage, W., Kefi, M. Z., Allain, P., et al. (2009). Cognitive inhibition and working memory in unipolar depression. *Journal of affective disorders*, *116*(1-2), 100–105.

Goldman-Rakic, P. S. (1995). Cellular basis of working memory. *Neuron*, *14*, 477–485.

Goldman-Rakic P.S. (1987) Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In: Plum F (ed) *Handbook of physiology, the nervous system, functions of the brain*. Bethesds.: American Physiological Society

Goldman-Rakic, P., & Leung H-C. *(2002). Functional architecture of the dorsolateral prefrontal cortex in monkeys and humans. In: Stuss. D.T., Knight R.T., (eds). Principle of frontal lobe function. Oxford: Oxford University Press*

Gollan, J., & Pane, H. (2008). Identifying differences in biased affective information processing in major depression. *Psychiatry research*, *159*, 18–24.

Golomb, J. D., McDavitt, J. R. B., Ruf, B. M., Chen, J. I., Saricicek, A., Maloney, K. H., Hu, J., et al.(2009). Enhanced visual motion perception in major depressive disorder. *The journal of neuroscience*, *29*(28), 9072–9077.

Gotlib, I. H., & Hamilton, J. P. (2008). Neuroimaging and Depression: Current Status and Unresolved Issues. *Current Directions in psychological science*, *17*(2), 159–163.

Gotlib, I. H., & Joormann, J. (2010). Cognition and depression: current status and future directions. *Annual review of clinical psychology*, *6*, 285–312.

Gotlib, I. H., Kasch, K. L., Traill, S., Joormann, J., Arnow, B. A., & Johnson, S. L. (2004). Coherence and specificity of information-processing biases in depression and social phobia. *Journal of abnormal psychology*, *113*(3), 386–398.

Gotlib, I., & Joormann, J. (2010). Cognition and Depression: Current Status and Future Directions. *Annual review of clinical psychology*, *27*(6), 285–312.

Gotlib, I., & Krasnoperova, E. (2004). Attentional biases for negative interpersonal stimuli in clinical depression. *Journal of abnormal psychology*, *113*(1), 127–135.

Gollan, J. K., McCloskey, M., Hoxha, D., & Coccaro, E. F. (2010). How do depressed and healthy adults interpret nuanced facial expressions?. *Journal of abnormal psychology*, *119*(4), 804-810

Grady, C. L. (2008). Cognitive neuroscience of aging. *Annals of the New York Academy of Sciences*, *1124*, 127–144.

Greenberg, P. E., Kessler, R. C., Birnbaum, H. G., Leong, S. A., Lowe, S. W., Berglund, P. A., & Corey-Lisle, P. K. (2003). The economic burden of depression in the United States: how did it change between 1990 and 2000? *The Journal of clinical psychiatry*, *64*(12), 1465–1475.

Griffin, I. C., & Nobre, A. C. (2003). Orienting attention to locations in internal representations. *Journal of cognitive neuroscience*, *15*(8), 1176–1194.

Grill-Spector, K., Sayres, R., & Ress, D. (2006). High-resolution imaging reveals highly selective nonface clusters in the fusiform face area. *Nature neuroscience*, *9*(9), 1177–1185.

Grossman, E. D., Battelli, L., & Pascual-Leone, A. (2005). Repetitive TMS over posterior STS disrupts perception of biological motion. *Vision research*, *45*(22), 2847–2853.

Gruber, O., & Goschke, T. (2004). Executive control emerging from dynamic interactions between brain systems mediating language, working memory and attentional processes. *Acta psychologica*, *115*(2-3), 105–121.

Gruber, O., Zilles, D., Kennel, J., Gruber, E., & Falkai, P. (2011). A systematic experimental neuropsychological investigation of the functional integrity of working memory circuits in major depression. *European archives of psychiatry and clinical neuroscience*, *261*(3), 179–184.

Gschwind, M., Pourtois, G., Schwartz, S., Van De Ville, D., & Vuilleumier, P. (2012). White-matter connectivity between face-responsive regions in the human brain. *Cerebral cortex*, *22*(7), 1564–1576.

Gutchess, A. H., Welsh, R. C., Hedden, T., Bangert, A., Minear, M., Liu, L. L., & Park, D. C. (2005). Aging and the neural correlates of successful picture encoding: frontal activations compensate for decreased medial-temporal activity. *Journal of cognitive neuroscience*, *17*(1), 84–96.

Hajek, T., Kopecek, M., Kozeny, J., Gunde, E., Alda, M., & Höschl, C. (2009). Amygdala volumes in mood disorders-meta-analysis of magnetic resonance volumetry studies. *Journal of affective disorders*, *115*(3), 395–410.

Haldane, M., & Frangou, S. (2006). Functional neuroimaging studies in mood disorders. *Acta Neuropsychiatrica*, *18*(2), 88-99.

Haldane, M., Cunningham, G., Androutsos, C., & Frangou, S. (2008). Structural brain correlates of response inhibition in Bipolar Disorder I. *Journal of psychopharmacology*, *22*(2), 138–43.

Hamidi, M., Drevets, W. C., & Price, J. L. (2004). Glial reduction in amygdala in major depressive disorder is due to oligodendrocytes. *Biological psychiatry*, *55*(6), 563-569.

Hamilton, J. P., & Gotlib, I. H. (2008). Neural substrates of increased memory sensitivity for negative stimuli in major depression. *Biological psychiatry*, *63*(12), 1155–1562.

Hamilton, J. P., Lemus, M. G., Johnson, R. F., & Gotlib, I. H. (2012). Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of baseline activation and neural response data. A*merican journal of psychiatry*, *169*(7), 693–704.

Hamilton, J., Siemer, M., & Gotlib, I. (2008). Amygdala volume in Major Depressive Disorder: A meta-analysis of magnetic resonance imaging studies. *Molecular psychiatry*, *13*(11), 993–1000.

Hammar, A., & Ardal, G. (2009). Cognitive functioning in major depression-a summary. *Frontiers in human neuroscience*, *3*(26).

Han, X., Berg, A. C., Oh, H., Samaras, D., & Leung, H. C. (In Press). Multi-voxel pattern analysis of selective representation of visual working memory in ventral temporal and occipital regions. *Neuroimage*.

Hartlage, S., Alloy, L. B., Vázquez, C., & Dykman, B. (1993). Automatic and effortful processing in depression. *Psychological bulletin*, *113*(2), 247–78. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8451334

Harvey, P. O., Le Bastard, G., Pochon, J. B., Levy, R., Allilaire, J. F., Dubois, B., & Fossati, P. (2004). Executive functions and updating of the contents of working memory in unipolar depression. *Journal of psychiatric research*, *38*(6), 567–576.

Harvey, P. O., Fossati, P., Pochon, J.-B., Levy, R., Lebastard, G., Lehéricy, S., Allilaire, J.-F., et al. (2005). Cognitive control and brain resources in major depression: an fMRI study using the n-back task. *Neuroimage*, *26*(3), 860–869.

Hasher, L, Zacks, R., & May, C. (1999). Inhibitory control, circadian arousal, and age. In D. Gopher & A. Koriat (Eds.), *Attention and Performance* (XVII). Cambridge, MA: MIT Press.

Hasher, Lynn, & Zacks, Rose, T. (1988). Working memory, comprehension, and aging: A review and a new view. *Psychology of learning & motivation (V22)*. Cambridge, MA: MIT Press.

Hasselbalch, B. J., Knorr, U., & Kessing, L. V. (2011). Cognitive impairment in the remitted state of unipolar depressive disorder: a systematic review. *Journal of affective disorders*, *134*(1-3), 20–31.

Hastings, R. S., Parsey, R. V, Oquendo, M. a, Arango, V., & Mann, J. J. (2004). Volumetric analysis of the prefrontal cortex, amygdala, and hippocampus in major depression. *Neuropsychopharmacology*, *29*(5), 952–959.

Healey, M. K., Campbell, K. L., Hasher, L., & Ossher, L. (2010). Direct evidence for the role of inhibition in resolving interference in memory. *Psychological science*, *21*(10), 1464-1470.

Hertel, P. T., & Rude, S. S. (1991). Depressive deficits in memory: focusing attention improves subsequent recall. *Journal of experimental psychology. General*, *120*(3), 301–9.

Hertel P. T. (2004). Memory for emotional and nonemotional events in depression: a question of habit? In: Reisberg D, Hertel P, (eds). *Memory and Emotion*. New York: Oxford Univ Press.

Herrington, J., Taylor, J., & Grupe, D. (2011). Bidirectional communication between amygdala and fusiform gyrus during facial recognition. *Neuroimage*, *56*(4), 2348–2355.

Herzog, A. G., & Van Hoesen, G. W. (1976) Temporal neocortical afferent connections to the amygdala in the rhesus monkey. *Brain research*, 115, 57–69.

Hickie, I. B., Naismith, S. L., Ward, P. B., Scott, E. M., Mitchell, P. B., Schofield, P. R., Scimone, A., et al. (2007). Serotonin transporter gene status predicts caudate nucleus but not amygdala or hippocampal volumes in older persons with major depression. *Journal of affective disorders*, *98*(1-2), 137–142.

Hoffman, E. a, & Haxby, J. V. (2000). Distinct representations of eye gaze and identity in the distributed human neural system for face perception. *Nature neuroscience*, *3*(1), 80–84.

Holtzheimer, P. E., & Mayberg, H. S. (2011). Stuck in a rut: rethinking depression and its treatment. *Trends in neurosciences*, *34*(1), 1–9.

Holtzheimer, P. E., Kelley, M. E., Gross, R. E., Filkowski, M. M., Garlow, S. J., Barrocas, A., Wint, D., et al. (2012). Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. *Archives of general psychiatry*, *69*(2), 150–158.

Hyman, S. E. (2010). The Diagnosis of Mental Disorders: The Problem of Reification. *Annual review of clinical psychology*, *6*(1), 155–179.

Insel, T., Cuthbert, B. N., Garvey, M., Heinssen, R., Pine, D. S., Sanislow, C., & Wang, P. (2010). Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *American journal of psychiatry*, *167*(7), 748–751.

Insel, T. (2013, April 29), Director's Blog: Transforming Diagnosis [Blog Post]. Retrieved from: http://www.nimh.nih.gov/about/director/2013/transforming-diagnosis.shtml

Ishai, A. (2008). Let's face it: it's a cortical network. *Neuroimage*, *40*(2), 415–419.

Ishai, A., Schmidt, C. F., & Boesiger, P. (2005). Face perception is mediated by a distributed cortical network. *Brain research bulletin*, *67*(1-2), 87–93.

Johnson, S. C., Baxter, L. C., Susskind-Wilder, L., Connor, D. J., Sabbagh, M. N., & Caselli, R. J. (2004). Hippocampal adaptation to face repetition in healthy elderly and mild cognitive impairment. *Neuropsychologia*, *42*(7), 980–989

Johnson, J. D., McDuff, S. G. R., Rugg, M. D., & Norman, K. a. (2009). Recollection, familiarity, and cortical reinstatement: a multivoxel pattern analysis. *Neuron*, *63*(5), 697–708.

Johnstone T, van Reekum C, Urry H, Kalin N, Davidson R. (2007). Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. *Journal of neuroscience*, 27, 8877–8884.

Jonas, J., Descoins, M., Koessler, L., Colnat-Coulbois, S., Sauvée, M., Guye, M., Vignal, J.-P., et al. (2012). Focal electrical intracerebral stimulation of a face-sensitive area causes transient prosopagnosia. n*euroscience*, *222*, 281–288.

Jonides, J., & Nee, D. E. (2006). Brain mechanisms of proactive interference in working memory. *Neuroscience*, *139*(1), 181–193.

Jonides, J., Lewis, R. L., Nee, D. E., Lustig, C. a, Berman, M. G., & Moore, K. S. (2008). The mind and brain of short-term memory, *Annual reviews of neuroscience*, 59, 193-224.

Joormann, J. (2004). Attentional bias in dysphoria: The role of inhibitory processes. *Cognition & emotion*, *18*(1), 125–147.
Joormann, J. (2006). Differential Effects of Rumination and Dysphoria on the Inhibition of Irrelevant Emotional Material: Evidence from a Negative Priming Task. *Cognitive therapy and research*, *30*(2), 149–160.
Joormann, J., & Gotlib, I. H. (2007). Selective attention to emotional faces following recovery from depression. *Journal of abnormal psychology*, *116*(1), 80–85.
Joormann, J., & Gotlib, I. H. (2008). Updating the contents of working memory in depression: interference from irrelevant negative material. *Journal of abnormal psychology*, *117*(1), 182–92.
Joormann, J., Nee, D. E., Berman, M. G., Jonides, J., & Gotlib, I. H. (2010). Interference resolution in major depression. *Cognitive, affective & behavioral neuroscience*, *10*(1), 21–33.
Joormann, J., Talbot, L., & Gotlib, I. H. (2007). Biased processing of emotional information in girls at risk for depression. *Journal of abnormal psychology*, *116*(1), 135–143.
Joormann, J., Yoon, K. L., & Zetsche, U. (2007). Cognitive inhibition in depression. *Applied and preventive psychology*, *12*(3), 128–139.
Kanwisher, N, McDermott, J., & Chun, M. M. (1997). The fusiform face area: a module in human extrastriate cortex specialized for face perception. *The Journal of neuroscience*, *17*(11), 4302–4311.
Kanwisher, Nancy, & Yovel, G. (2006). The fusiform face area: a cortical region specialized for the perception of faces. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, *361*(1476), 2109–2128.
Katz, M. M., Bowden, C. L., & Frazer, A. (2010). Rethinking depression and the actions of antidepressants: uncovering the links between the neural and behavioral elements. *Journal of affective disorders*, *120*(1-3), 16–23.
Kendell, R., & Jablensky, A. (2003). Reviews and overviews of psychiatric diagnoses. *American journal of psychiatry*, *160*(1), 4–12.
Kessler, R. C., Angermeyer, M., Anthony, J. C., De Graaf, R.O.N., Demyttenaere, K., Gasquet, I., et al., (2007). Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World psychiatry*, *6*(3), 168-176.
Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., Rush, A. J., et al. (2003). The epidemiology of major depressive disorder results from the national comorbidity survey replication (NCS-R). *Journal of the American Medical Association*, *289*(23), 3095–3105.
Kerestes, R., Ladouceur, C. D., Meda, S., Nathan, P. J., Blumberg, H. P., Maloney, K., Ruf, B., et al. (2012). Abnormal prefrontal activity subserving attentional control of emotion in remitted depressed patients during a working memory task with emotional distracters. *Psychological medicine*, *42*(1), 29–40.
Ketter, T. a, Kimbrell, T. a, George, M. S., Dunn, R. T., Speer, A. M., Benson, B. E., Willis, M. W., et al. (2001). Effects of mood and subtype on cerebral glucose metabolism in treatment-resistant bipolar disorder. *Biological psychiatry*, *49*(2), 97–109.
Kirchner, W. (1958). Age differences in short-term retention of rapidly changing information. *Journal of experimental psychology*, 4, 352–358.
Kleinhans, N., & Richards, T. (2010). Association between amygdala response to emotional faces and social anxiety in autism spectrum disorders. *Neuropsychologia*, *48*(12), 3665–3670.
Koenigs, M., & Grafman, J. (2009). The functional neuroanatomy of depression: distinct roles for ventromedial and dorsolateral prefrontal cortex. *Behavioural brain research*, *201*(2), 239–243.
Koolschijn, P. C. M. P., Van Haren, N. E. M., Lensvelt-Mulders, G. J. L. M., Hulshoff Pol, H. E., & Kahn, R. S. (2009). Brain volume abnormalities in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. *Human brain mapping*, *30*(11), 3719–3735.
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*(1), 138–145.
Krishnan, V., & Nestler, E. J. (2008). The molecular neurobiology of depression. *Nature*, *455*(7215), 894–902.
Kujawa, A., Hajcak, G., Torpey, D., Kim, J., & Klein, D. N. (2012). Electrocortical reactivity to emotional faces in young children and associations with maternal and paternal depression. *Journal of child psychology and psychiatry, and allied disciplines*, *53*(2), 207–215.
Kujawa, A. J., Torpey, D., Kim, J., Hajcak, G., Rose, S., Gotlib, I. H., & Klein, D. N. (2011). Attentional biases for emotional faces in young children of mothers with chronic or recurrent depression. *Journal of abnormal child psychology*, *39*(1), 125–35.

Lacerda, A. L., Nicoletti, M. A., Brambilla, P., Sassi, R. B., Mallinger, A. G., Frank, E., … et al. (2003). Anatomical MRI study of basal ganglia in major depressive disorder. *Psychiatry Research: Neuroimaging*, *124*(3), 129-140.

Lawrence, N. S., Williams, A. M., Surguladze, S., Giampietro, V., Brammer, M. J., Andrew, C., Frangou, S., et al. (2004). Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. *Biological psychiatry*, *55*(6), 578–587.

Lee, B.-T., Seok, J.-H., Lee, B.-C., Cho, S. W., Yoon, B.-J., Lee, K.-U., Chae, J.-H., et al. (2008). Neural correlates of affective processing in response to sad and angry facial stimuli in patients with major depressive disorder. *Progress in neuro-psychopharmacology & biological psychiatry*, *32*(3), 778–785.

Lee, R. S. C., Hermens, D. F., Porter, M. a, & Redoblado-Hodge, M. A. (2012). A meta-analysis of cognitive deficits in first-episode Major Depressive Disorder. *Journal of affective disorders*, *140*(2), 113–124.

Leppänen, J. M. (2006). Emotional information processing in mood disorders: a review of behavioral and neuroimaging findings. *Current opinion in psychiatry*,*19*(1), 34-39.

Lepsien, J., & Nobre, A. C. (2006). Cognitive control of attention in the human brain: insights from orienting attention to mental representations. *Brain research*, *1105*(1), 20–31.

Lepsien, J., & Nobre, A. C. (2007). Attentional modulation of object representations in working memory. *Cerebral cortex*, *17*(9), 2072–2083.

Leyman, L., De Raedt, R., Vaeyens, R., & Philippaerts, R. M. (2011). Attention for emotional facial expressions in dysphoria: an eye-movement registration study. *Cognition & emotion*, *25*(1), 111–120.

Leung, H.-C., Gore, J. C., & Goldman-Rakic, P. S. (2002). Sustained mnemonic response in the human middle frontal gyrus during on-line storage of spatial memoranda. *Journal of cognitive neuroscience*, *14*(4), 659–671.

Leung, H.-C., Gore, J. C., & Goldman-Rakic, P. S. (2005). Differential anterior prefrontal activation during the recognition stage of a spatial working memory task. *Cerebral cortex*, *15*(11), 1742–1749.

Leung, H.-C., Seelig, D., & Gore, J. C. (2004). The effect of memory load on cortical activity in the spatial working memory circuit. Cognitive, Affective & Behavioral Neuroscience, 4(4), 553-563.

Leung, H. C., & Zhang, J. X. (2004). Interference resolution in spatial working memory. *Neuroimage*, 23, 1013–1019.

Lim, K., & Ardekani, B. (2006). Voxelwise Correlational Analyses of White Matter Integrity in Multiple Cognitive Domains in Schizophrenia. *The American journal of psychiatry*, *163*(11), 2008–2010.

Linden, D. E. J., Bittner, R. a., Muckli, L., Waltz, J. a., Kriegeskorte, N., Goebel, R., Singer, W., et al. (2003). Cortical capacity constraints for visual working memory: dissociation of fMRI load effects in a fronto-parietal network. *Neuroimage*, *20*(3), 1518–1530.

Linville, P. (1996). Attention inhibition: Does it underlie ruminative thought. In: Wyer, E. S. *Ruminative thoughts: Advances in social cognition IX*. Lawrence Erlbaum, Mahwah, New Jersey.

Logothetis, N. K., & Wandell, B. a. (2004). Interpreting the BOLD signal. *Annual review of physiology*, *66*, 735–769.

Lorenzetti, V., Allen, N. B., Fornito, A., & Yücel, M. (2009). Structural brain abnormalities in major depressive disorder: a selective review of recent MRI studies. *Journal of affective disorders*, *117*(1-2), 1–17.

Luciana, M., Collins, P. F., & Depue, R. a. (1998). Opposing roles for dopamine and serotonin in the modulation of human spatial working memory functions. *Cerebral cortex*, *8*(3), 218–26.

Lundqvist, D., Flykt, A., & Öhman, A. (1998). The Karolinska Directed Emotional Faces - KDEF, CD ROM from Department of Clinical Neuroscience, Psychology section, Karolinska Institutet.

MacLeod, C., Mathews, a, & Tata, P. (1986). Attentional bias in emotional disorders. *Journal of abnormal psychology*, *95*(1), 15–20.

MacQueen, G. M., Tipper, S. P., Young, L. T., Joffe, R. T., & Levitt, A. J. (2000). Impaired distractor inhibition on a selective attention task in unmedicated, depressed subjects. *Psychological medicine*, *30*(03), 557-564.

Manji, H. K., Drevets, W. C., & Charney, D. S. (2001b). The cellular neurobiology of depression. *Nature medicine*, *7*(5), 541–547.

Mannie, Z. N., Taylor, M. J., Harmer, C. J., Cowen, P. J., & Norbury, R. (2011). Frontolimbic responses to emotional faces in young people at familial risk of depression. *Journal of affective disorders*, *130*(1-2), 127–132.

Mathews, A., & MacLeod, C. (2005). Cognitive vulnerability to emotional disorders. *Annual review of clinical psychology*, *1*, 167–195.

Matthews, S., Simmons, A., Strigo, I., Gianaros, P., Yang, T., & Paulus, M. (2009). Inhibition-related activity in subgenual cingulate is associated with symptom severity in major depression. *Psychiatry research*, *172*(1), 1–6.

Matsuo, K., Glahn, D. C., Peluso, M. a M., Hatch, J. P., Monkul, E. S., Najt, P., Sanches, M., et al. (2007). Prefrontal hyperactivation during working memory task in untreated individuals with major depressive disorder. *Molecular psychiatry*, *12*(2), 158–166.

Mayberg, H. (1997). Limbic-cortical dysregulation: a proposed model of depression. *The Journal of neuropsychiatry and clinical neurosciences*, *9*(3), 471–481.

Mayberg, H. S., Liotti, M., Brannan, S. K., McGinnis, S., Mahurin, R. K., Jerabek, P. A., et al. (1999). Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *American Journal of Psychiatry*, *156*(5), 675-682.

Mayberg, H S, Brannan, S. K., Tekell, J. L., Silva, J. a, Mahurin, R. K., McGinnis, S., & Jerabek, P. a. (2000). Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. *Biological psychiatry*, *48*(8), 830–843.

Mayberg, Helen S., Lozano, A. M., Voon, V., McNeely, H. E., Seminowicz, D., Hamani, C., Schwalb, J. M., et al. (2005). Deep Brain Stimulation for Treatment-Resistant Depression. *Neuron*, *45*(5), 651–660.

Mayberg, H. S., Liotti, M., Brannan, S. K., McGinnis, S., Mahurin, R. K., Jerabek, P. a, Silva, J. A, et al. (1999). Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *The American journal of psychiatry*, *156*(5), 675–682.

Mazaika, P., Whitfield, S., Cooper, J.C. (2005). Detection and Repair of Transient Artifacts in fMRI Data. Presented at Human brain mapping, 2005

Mazaika, P., Whitfield-Gabrieli, S., Reiss, A. L. (2007). Artifact Repair for fMRI Data from High Motion Clinical Subjects. Presented at Human brain mapping, 2007.

Mazaika, P., Hoeft, F., Glover, G.H., Reiss, A. L. (2009). Methods and Software for fMRI Analysis for Clinical Subjects. Presented at Human brain mapping, 2009.

McDonald, A. J., Shammah- Lagnado, S. J., Shi, C., & Davis, M. (1999). Cortical afferents to the extended amygdala. *Annals of the New York Academy of Sciences*, *877*(1), 309-338.

McNab, F., & Klingberg, T. (2007). Prefrontal cortex and basal ganglia control access to working memory. *Nature neuroscience*, *11*(1), 103-107.

Miguel-Hidalgo, J., & Dubey, P. (2005). Unchanged packing density but altered size of neurofilament immunoreactive neurons in the prefrontal cortex in schizophrenia and major depression. *Schizophrenia research*, *76*, 159–171.

Miguel-Hidalgo, J., Wei, J., & Andrew, M. (2002). Glia Pathology in the Prefrontal Cortex in Alcohol Dependence with and without depressive symptoms. *Biological psychiatry*, *52*(12), 1121–1133.

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual review of neuroscience*, *24*, 167–202.

Minear, M. & Park, D.C. (2004). A lifespan database of adult facial stimuli. *Behavior research: Methods, instruments, & computers*, 36, 630-633.

Minzenberg, M. J., Laird, A. R., Thelen, S., Carter, C. S., & Glahn, D. C. (2009). Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Archives of general psychiatry*, *66*(8), 811–822.

Mitterschiffthaler, M. T., Kumari, V., Malhi, G. S., Brown, R. G., Giampietro, V. P., Brammer, M. J., Suckling, J., et al. (2003). Neural response to pleasant stimuli in anhedonia: an fMRI study. *Neuroreport*, *14*(2), 177–182.

Miyake, A., & Shah, P. (Eds.). (1999). *Mechanisms of Active Maintenance and Executive Control*. New York, NY: Cambridge University Press.

Mogg, K., & Bradley, B. P. (2005). Attentional Bias in Generalized Anxiety Disorder Versus Depressive Disorder. *Cognitive Therapy and Research*, *29*(1), 29–45.

Mogg, K., Bradley, B. P., & Williams, R. (1995). Attentional bias in anxiety and depression: The role of awareness. *British journal of clinical psychology*, *34*(1), 17-36.

Murray E. A., Bussey T. J., Wise S. P. (2000). Role of prefrontal cortex in a network for arbitrary visuomotor mapping. *Experimental. Brain Research*, 133(1), 114–129.

Murray, E., Wise, S., & Drevets, W. (2011). Localization of dysfunction in major depressive disorder: Prefrontal cortex and amygdala. *Biological psychiatry*, *69*(12), 43-54.

Murrough, J. W., Iacoviello, B., Neumeister, A., Charney, D. S., & Iosifescu, D. V. (2011). Cognitive dysfunction in depression: neurocircuitry and new therapeutic strategies. *Neurobiology of learning and memory*, *96*(4), 553-563.

Nasr, S., Liu, N., Devaney, K. J., Yue, X., Rajimehr, R., Ungerleider, L. G., & Tootell, R. B. H. (2011). Scene-selective cortical regions in human and nonhuman primates. *The Journal of neuroscience*, *31*(39), 13771–85.

Nee, D. E., Brown, J. W., Askren, M. K., Berman, M. G., Demiralp, E., Krawitz, A., & Jonides, J. (2013). A meta-analysis of executive components of working memory. *Cerebral cortex*, *23*(2), 264–282.

Nee, D. E., Jonides, J., & Berman, M. G. (2007). Neural mechanisms of proactive interference-resolution. *Neuroimage*, *38*(4), 740–751.
Nigg, J. T. (2000). On inhibition/disinhibition in developmental psychopathology: Views from cognitive and personality psychology and a working inhibition taxonomy. *Psychological Bulletin*, *126*(2), 220–246.
Nofzinger, E. a, Buysse, D. J., Germain, A., Price, J. C., Meltzer, C. C., Miewald, J. M., & Kupfer, D. J. (2005). Alterations in regional cerebral glucose metabolism across waking and non-rapid eye movement sleep in depression. *Archives of general psychiatry*, *62*(4), 387–396.
Nolen-Hoeksema, S., Morrow, J., & Fredrickson, B. L. (1993). Response styles and the duration of episodes of depressed mood. *Journal of abnormal psychology*, *102*(1), 20-28.
Nutt, D. (2006). The Role of Dopamine and Norepinephrine in Depression and Antidepressant Treatment. *Journal of Clinical psychiatry*, (6), 6–9.
Oberauer, K. (2001). Removing irrelevant information from working memory: A cognitive aging study with the modified Sternberg task. *Journal of experimental psychology: Learning, memory, and cognition*, *27*(4), 948–957.
Oberauer, K. (2002). Access to information in working memory: Exploring the focus of attention. *Journal of Experimental Psychology: Learning, memory, and cognition*, *28*(3), 411–421.
Oberauer, K (2009). Design for a Working Memory. *Psychology of learning and motivation*, 51, 45-100.
Oberauer, K., & Hein, L. (2012). Attention to Information in Working Memory. *Current directions in psychological science*, *21*(3), 164–169.
Ochsner, K. N., & Gross, J. J. (2005). The cognitive control of emotion. *Trends in cognitive sciences*, *9*(5), 242–249.
Oh, H., & Leung, H.-C. (2010). Specific and nonspecific neural activity during selective processing of visual representations in working memory. *Journal of cognitive neuroscience*, *22*(2), 292–306.
Öngür, D., Drevets, W., & Price, J. (1998). Glial reduction in the subgenual prefrontal cortex in mood disorders. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(October), 13290–13295.
Osaka, N., Osaka, M., Kondo, H., Morishita, M., Fukuyama, H., Shibasaki, H. (2004). The neural basis of executive function in working memory: an fMRI study based on individual differences. *Neuroimage*, *21*(2), 623–631.
Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. (2005). N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Human brain mapping*, *25*(1), 46–59.
Paelecke-Habermann, Y., Pohl, J., & Leplow, B. (2005). Attention and executive functions in remitted major depression patients. *Journal of affective disorders*, *89*(1-3), 125–135.
Palaniyappan, L., Al-Radaideh, A., Mougin, O., Gowland, P., & Liddle, P. F. (In Press). Combined White Matter Imaging Suggests Myelination Defects in Visual Processing Regions in Schizophrenia. *Neuropsychopharmacology*.
Pandya, D. N., & Seltzer, B. (1982). Intrinsic connections and architectonics of posterior parietal cortex in the rhesus monkey. *The Journal of comparative neurology*, *204*(2), 196–210.
Park, S., & Chun, M. M. (2009). Different roles of the parahippocampal place area (PPA) and retrosplenial cortex (RSC) in panoramic scene perception. *Neuroimage*, *47*(4), 1747–1756.
Park, D. C., Polk, T. a, Park, R., Minear, M., Savage, A., & Smith, M. R. (2004). Aging reduces neural specialization in ventral visual cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(35), 13091–13095.
Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: aging and neurocognitive scaffolding. *Annual review of psychology*, *60*, 173–196.
Park, D. C., Welsh, R. C., Marshuetz, C., Gutchess, A. H., Mikels, J., Polk, T. a, Noll, D. C., et al. (2003). Working memory for complex scenes: age differences in frontal and hippocampal activations. *Journal of cognitive neuroscience*, *15*(8), 1122–1134.
Park, J., Carp, J., Hebrank, A., Park, D. C., & Polk, T. a. (2010). Neural specificity predicts fluid processing ability in older adults. *The Journal of Neuroscience : the official journal of the Society for Neuroscience*, *30*(27), 9253–9259.
Passingham, R. E., & Wise, S. P. (2012). *The neurobiology of the prefrontal cortex: anatomy, evolution, and the origin of Insight* (Vol. 50): Oxford: Oxford University Press.
Passingham, R. E., Toni I., Rushworth M. F. (2000). Specialization within the prefrontal cortex: the ventral prefrontal cortex and associative learning. *Experimental Brain Research*, 133(1), 103–113.
Persson, J., Nyberg, L., Lind, J., Larsson, A., Nilsson, L.-G., Ingvar, M., & Buckner, R. L. (2006). Structure-function correlates of cognitive decline in aging. *Cerebral cortex*, *16*(7), 907–915.
Pessoa, L., & Adolphs, R. (2010). Emotion processing and the amygdala: from a "low road" "many roads" of evaluating biological significance. *Nature Reviews Neuroscience*, *11*(11), 773–783.

Pessoa, L., McKenna, M., Gutierrez, E., & Ungerleider, L. G. (2002). Neural processing of emotional faces requires attention. *Proceedings of the National Academy of Sciences of the United States of America*, *99*(17), 11458–11463.
Petrides, M. (2000). Dissociable roles of mid-dorsolateral prefrontal and anterior inferotemporal cortex in visual working memory. *The Journal of neuroscience*, *20*(19), 7496–7503.
Petrides, M., & Milner, B. (1982). Deficits on subject-ordered tasks after frontal-and temporal-lobe lesions in man. *Neuropsychologia*, *20*(3), 249-262.
Petrides, M., & Pandya, D. N. (1984). Projections to the frontal cortex from the posterior parietal region in the rhesus monkey. *The Journal of comparative neurology*, *228*(1), 105–116.
Petrides, M., & Pandya, D. N. (1988). Association fiber pathways to the frontal cortex from the superior temporal region in the rhesus monkey. *Journal of Comparative Neurology*, *273*(1), 52-66.
Petrides, M., & Pandya, D. N. (1999). Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. *The European journal of neuroscience*, *11*(3), 1011–1036.
Phelps, E. a, & LeDoux, J. E. (2005). Contributions of the amygdala to emotion processing: from animal models to human behavior. *Neuron*, *48*(2), 175–187.
Pitcher, D., Walsh, V., & Duchaine, B. (2011). The role of the occipital face area in the cortical face perception network. *Experimental brain research*, *209*(4), 481–493.
Poldrack, R. A. (2007). Region of interest analysis for fMRI. *Social cognitive and affective neuroscience*, *2*(1), 67–70.
Porrino, L. J., Crane, A. M., Goldman-Rakic, P. S. (1981) Direct and indirect pathways from the amygdala to the frontal lobe in rhesus monkeys. Journal of comparative neurology, 198, 121–136.
Postle, B. R., Druzgal, T. J., & D'Esposito, M. (2003). Seeking the neural substrates of visual stimuli, Cortex, *3*(1936), 927–946.
Postle, B. R. (2006). Working memory as an emergent property of the mind and brain. *Neuroscience*, *139*(1), 23–38.
Postle, B. R., Zarahn, E., & D'Esposito, M. (2000). Using event-related fMRI to assess delay-period activity during performance of spatial and nonspatial working memory tasks. *Brain research. Brain research protocols*, *5*(1), 57–66.
Pourtois, G., Sander, D., Andres, M., Grandjean, D., Reveret, L., Olivier, E., & Vuilleumier, P. (2004). Dissociable roles of the human somatosensory and superior temporal cortices for processing social face signals. *The European journal of neuroscience*, *20*(12), 3507–3515.
Price, J. L., & Drevets, W. C. (2010). Neurocircuitry of mood disorders. *Neuropsychopharmacology*, *35*(1), 192–216.
Rajah, M. N., & D'Esposito, M. (2005). Region-specific changes in prefrontal function with age: a review of PET and fMRI studies on working and episodic memory. *Brain*, *128*(9), 1964–1683.
Rajkowska, G. (2003). Depression: What we can learn from postmortem studies. *The Neuroscientist*, *9*(4), 273-284.
Rajkowska, G., & Miguel-Hidalgo, J. (2005). Prominent reduction in pyramidal neurons density in the orbitofrontal cortex of elderly depressed patients. *Biological psychiatry*, *58*(4), 297–306.
Rajkowska, G., Halaris, A., & Selemon, L. D. (2001). Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. *Biological Psychiatry*, *49*(9), 741-752.
Rajkowska, G, Miguel-Hidalgo, J. J., Wei, J., Dilley, G., Pittman, S. D., Meltzer, H. Y., et al. (1999). Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. *Biological Psychiatry*, *45*(9), 1085-1098
Ranganath, C. (2010). A unified framework for the functional organization of the medial temporal lobes and the phenomenology of episodic memory. *Hippocampus*, *20*(11), 1263–1290.
Ranganath, C., & Ritchey, M. (2012). Two cortical systems for memory-guided behaviour. *Nature reviews. Neuroscience*, *13*(10), 713–726.
Ranganath, C., Yonelinas, A. P., Cohen, M. X., Dy, C. J., Tom, S. M., & D'Esposito, M. (2004). Dissociable correlates of recollection and familiarity within the medial temporal lobes. *Neuropsychologia*, *42*(1), 2–13.
Ranganath, C., & D'Esposito, M. (2005). Directing the mind's eye: prefrontal, inferior and medial temporal mechanisms for visual working memory. *Current opinion in neurobiology*, *15*(2), 175–182.
Regenold, W. T., Phatak, P., Marano, C. M., Gearhart, L., Viens, C. H., & Hisley, K. C. (2007). Myelin staining of deep white matter in the dorsolateral prefrontal cortex in schizophrenia, bipolar disorder, and unipolar major depression. *Psychiatry research*, *151*(3), 179-188.
Remy, P., Doder, M., Lees, A., Turjanski, N., & Brooks, D. (2005). Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. *Brain*, *128*(6), 1314–1322.

Reuter-Lorenz, P. A., & Cappell, K. A. (2008). Neurocognitive aging and the compensation hypothesis. *Current directions in psychological science*, *17*(3), 177-182.
Ridout, N., Astell, A., & Reid, I. (2003). Memory bias for emotional facial expressions in major depression. *Cognition & emotion*, *17*(1), 101–122.
Rinck, M., & Becker, E. S. (2005). A comparison of attentional biases and memory biases in women with social phobia and major depression. *Journal of abnormal psychology*, *114*(1), 62–74.
Robinson, O. J., Cools, R., Carlisi, C. O., Sahakian, B. J., & Drevets, W. C. (2012). Ventral striatum response during reward and punishment reversal learning in unmedicated major depressive disorder. *American journal of psychiatry*, *169*(2), 152–159.
Rogers, M. A., Kasai, K., Koji, M., Fukuda, R., Iwanami, A., Nakagome, K., Fukuda, M., et al. (2004). Executive and prefrontal dysfunction in unipolar depression: a review of neuropsychological and imaging evidence. *Neuroscience research*, *50*(1), 1–11.
Rose, E. J., & Ebmeier, K. P. (2006). Pattern of impaired working memory during major depression. *Journal of affective disorders*, *90*(2-3), 149–161.
Rose, E. J., Simonotto, E., & Ebmeier, K. P. (2006). Limbic over-activity in depression during preserved performance on the n-back task. *Neuroimage*, *29*(1), 203–215.
Rottenberg, J., Hildner, J., & Gotlib, I. (2006). Idiographic autobiographical memories in major depressive disorder. *Cognition & emotion*, *20*(1), 114–128.
Rubin, E., Sackeim, H.A., Prohovnik, I., Moeller, J. R., Schnur D. B., & Mukherjee, S. (1995) Regional cerebral blood flow in mood disorders: IV. Comparison of mania and depression. *Psychiatry Research, 61*, 1–10
Rush, A.J., Gullion, C.M., Basco, M.R., Jarrett, R.B. & Trivedi, M.H. (1996) The inventory of depressive symptomatology (IDS): Psychometric properties. *Psychological Medicine*, 26, 477-486.
Russell, B. C., Torralba, A., Murphy, K. P., & Freeman, W. T. (2007). LabelMe: A Database and Web-Based Tool for Image Annotation. *International journal of computer vision*, *77*(1-3), 157–173.
Sabatinelli, D., Bradley, M. M., Fitzsimmons, J. R., & Lang, P. J. (2005). Parallel amygdala and inferotemporal activation reflect emotional intensity and fear relevance. *Neuroimage*, *24*(4), 1265–1270.
Sah, P., Faber, E. S. L., Lopez De Armentia, M., & Power, J. (2003). The amygdaloid complex: anatomy and physiology. *Physiological reviews*, *83*(3), 803–834.
Samanez-Larkin, G. R., & D'Esposito, M. (2008). Group comparisons: imaging the aging brain. *Social cognitive and affective neuroscience*, *3*(3), 290–297.
Salzman, C. D., & Fusi, S. (2010). Emotion, cognition, and mental state representation in amygdala and prefrontal cortex. *Annual review of neuroscience*, *33*, 173-202.
Sanacora, G., Treccani, G., & Popoli, M. (2012). Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. *Neuropharmacology*, *62*(1), 63-77.
Sandi, C. (2011). Glucocorticoids act on glutamatergic pathways to affect memory processes. *Trends in neurosciences*, *34*(4), 165–176.
Saxe, R., Brett, M., & Kanwisher, N. (2006). Divide and conquer: a defense of functional localizers. *Neuroimage*, *30*(4), 1088–1099.
Schaefer, A., & Gray, J. (2007). A role for the human amygdala in higher cognition. *Reviews in the Neurosciences*, *18*, 355–363.
Schmitz, T. W., De Rosa, E., & Anderson, A. K. (2009). Opposing influences of affective state valence on visual cortical encoding. *The Journal of neuroscience*, *29*(22), 7199–7207.
Seamans, J. K., & Yang, C. R. (2004). The principal features and mechanisms of dopamine modulation in the prefrontal cortex, *Progress in neurobiology*,*74*(1), 1-58
Seminowicz, D. A., Mayberg, H. S., McIntosh, A. R., Goldapple, K., Kennedy, S., Segal, Z., & Rafi-Tari, S. (2004). Limbic-frontal circuitry in major depression: a path modeling metanalysis. *Neuroimage*, *22*(1), 409–418.
Sheline, Y. I., Barch, D. M., Donnelly, J. M., Ollinger, J. M., Snyder, A Z., & Mintun, M. A. (2001). Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biological psychiatry*, *50*(9), 651–658.
Simmons, W. K., Bellgowan, P. S., & Martin, A. (2007). Measuring selectivity in fMRI data. *Nature neuroscience*,*10*(1), 4-5.
Smith, J. D., Tracy, J. I., & Murray, M. J. (1993). Depression and category learning. *Journal of experimental psychology. General*, *122*(3), 331–346.
Squire, L. R., Stark, C. E. L., & Clark, R. E. (2004). The medial temporal lobe. *Annual review of neuroscience*, *27*, 279–306.

Spielberger, C. D., Gorsuch, R. L., Lushene, R., Vagg, P. R., & Jacobs, G. A. (1983). *Manual for the State-Trait Anxiety Inventory*. Palo Alto: Consulting Psychologists Press.
Stockmeier, C., & Mahajan, G. (2004). Cellular changes in the postmortem hippocampus in Major Depression. *Biological psychiatry*, *56*(9), 640–650.
Stuhrmann, A., Suslow, T., & Dannlowski, U. (2011). Facial emotion processing in major depression: a systematic review of neuroimaging findings. *Biology of mood & anxiety disorders*, *1*(1), 10.
Stuss, D. T., and Knight, R. T. (2013). *Principles of frontal lobe function*. Oxford: Oxford University Press.
Surguladze, S., Brammer, M. J., Keedwell, P., Giampietro, V., Young, A. W., Travis, M. J., Williams, S. C. R., et al. (2005). A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. *Biological psychiatry*, *57*(3), 201–209.
Suslow, T., Konrad, C., Kugel, H., Rumstadt, D., Zwitserlood, P., Schöning, S., Ohrmann, P., et al. (2010). Automatic mood-congruent amygdala responses to masked facial expressions in major depression. *Biological psychiatry*, *67*(2), 155–160.
Takei, Y., Kumano, S., Hattori, S., Uehara, T., Kawakubo, Y., Kasai, K., Fukuda, M., et al. (2009). Preattentive dysfunction in major depression: a magnetoencephalography study using auditory mismatch negativity. *Psychophysiology*, *46*(1), 52–61.
Tham, M. W., Woon, P. S., Sum, M. Y., Lee, T.-S., & Sim, K. (2011). White matter abnormalities in major depression: evidence from post-mortem, neuroimaging and genetic studies. *Journal of affective disorders*, *132*(1-2), 26–36.
Thomas, E. J., & Elliott, R. (2009). Brain imaging correlates of cognitive impairment in depression. *Frontiers in human neuroscience*, *3*(30).
Tipper, S. (1985). The negative priming effect: inhibitory priming by ignored objects. *The Quarterly Journal of Experimental Psychology*, *37a*, 571–590.
Tipper, S. P. (2001). Does negative priming reflect inhibitory mechanisms ? A review and integration of conflicting views. *The quarterly journal of experimental psychology*, *54.4*(2), 321–343.
Todd, J. J., & Marois, R. (2004). Capacity limit of visual short-term memory in human posterior parietal cortex. *Nature*, *428*(6984), 751–754.
Toni, I., Ramnani, N., Josephs, O., Ashburner, J., & Passingham, R. E. (2001). Learning arbitrary visuomotor associations: temporal dynamic of brain activity. *Neuroimage*, *14*(5), 1048–1057.
Ungerleider, L. G., Courtney, S. M., & Haxby, J. V. (1998). A neural system for human visual working memory. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(3), 883–890.
Unsworth, N., Heitz, R. P., Schrock, J. C., & Engle, R. W. (2005). An automated version of the operation span task. *Behavior research methods*, *37*(3), 498–505.
Uranova, N. A., Vostrikov, V. M., Orlovskaya, D. D., & Rachmanova, V. I. (2004). Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. *Schizophrenia research*, *67*(2), 269-275.
Uranova, N., Orlovskaya, D., Vikhreva, O., Zimina, I., Kolomeets, N., Vostrikov, V., & Rachmanova, V. (2001). Electron microscopy of oligodendroglia in severe mental illness. *Brain research bulletin*, *55*(5), 597-610.
Van Strien, N. M., Cappaert, N. L. M., & Witter, M. P. (2009). The anatomy of memory: an interactive overview of the parahippocampal-hippocampal network. *Nature reviews neuroscience*, *10*(4), 272–282.
Van Vreeswijk, M. F., & De Wilde, E. J. (2004). Autobiographical memory specificity, psychopathology, depressed mood and the use of the Autobiographical Memory Test: A meta-analysis. *Behaviour research and therapy*, *42*(6), 731-743.
Vasic, N., Walter, H., Sambataro, F., & Wolf, R. C. (2009). Aberrant functional connectivity of dorsolateral prefrontal and cingulate networks in patients with major depression during working memory processing. *Psychological medicine*, *39*(6), 977–987.
Victor, T., Furey, M., & Fromm, S. (2010). Relationship of emotional processing to masked faces in the amygdala to mood state and treatment in major depressive disorder. *Archives of General Psychiatry, 67*(11), 1128–1138.
Vuilleumier, P., Richardson, M. P., Armony, J. L., Driver, J., & Dolan, R. J. (2004). Distant influences of amygdala lesion on visual cortical activation during emotional face processing. *Nature neuroscience*, *7*(11), 1271–1278.
Wager, T. D., Sylvester, T. C. C., Lacey, S. C., Nee, E., Franklin, M., & Jonides, J. (2005). Common and unique components of response inhibition revealed by fMRI. *Neuroimage*, *27*, 323–340.
Walsh, N. D., Kim, J., Andrew, C. M., Pich, E. M., Williams, P. M., Reed, L. J., & Mitterschiffthaler, M. T. (2004). Attenuation of the Neural Response to Sad Faces in Major Depression by Antidepressant Treatment. *Archives of general psychiatry*, *61*, 877–889.

Walsh, N. D., Williams, S. C. R., Brammer, M. J., Bullmore, E. T., Kim, J., Suckling, J., Mitterschiffthaler, M. T., et al. (2007). A longitudinal functional magnetic resonance imaging study of verbal working memory in depression after antidepressant therapy. *Biological psychiatry*, *62*(11), 1236–1243.

Walter, H, Vasic, N., Höse, A., Spitzer, M., & Wolf, R. (2007). Working memory dysfunction in schizophrenia compared to healthy controls and patients with depression: Evidence from event-related fMRI. *Neuroimage*, *35*(4).

Walter, H., Wolf, R. C., Spitzer, M., & Vasic, N. (2007b). Increased left prefrontal activation in patients with unipolar depression: an event-related, parametric, performance-controlled fMRI study. *Journal of affective disorders*, *101*(1-3), 175-85.

Wang, L., LaBar, K. S., Smoski, M., Rosenthal, M. Z., Dolcos, F., Lynch, T. R., Krishnan, R. R., et al. (2008). Prefrontal mechanisms for executive control over emotional distraction are altered in major depression. *Psychiatry research*, *163*(2), 143–155.

Wang, M., Vijayraghavan, S., & Goldman-Rakic, P. S. (2004). Selective D2 receptor actions on the functional circuitry of working memory. *Science signaling*, *303*(5659), 853-856.

Werner, N. S., Meindl, T., Materne, J., Engel, R. R., Huber, D., Riedel, M., Reiser, M., et al. (2009). Functional MRI study of memory-related brain regions in patients with depressive disorder. *Journal of affective disorders*, *119*(1-3), 124–131.

Westerhausen, R., Kompus, K., & Hugdahl, K. (2011). Impaired cognitive inhibition in schizophrenia: a meta-analysis of the Stroop interference effect. *Schizophrenia research*, *133*(1-3), 172–81.

The White House. (2013, April 2). Fact Sheet: BRAIN Initiative [Press Release]. Retrieved from: http://www.whitehouse.gov/the-press-office/2013/04/02/fact-sheet-brain-initiative

Willner, P., Scheel-Krüger, J., & Belzung, C. (In Press). The neurobiology of depression and antidepressant action. *Neuroscience & biobehavioral Reviews*.

Witt, S. T., & Stevens, M. C. (2013). fMRI task parameters influence hemodynamic activity in regions implicated in mental set switching. *Neuroimage*, 65, 1139-1151.

Wolf, R. C., & Walter, H. (2005). Evaluation of a novel event-related parametric fMRI paradigm investigating prefrontal function. *Psychiatry research*, *140*(1), 73–83.

Xiao, D., & Barbas, H. (2006b). Pathways for emotions and memory I. Input and output zones linking the anterior thalamic nuclei with prefrontal cortices in the rhesus monkey. *Thalamus and Related Systems*, *2*(01), 21-32

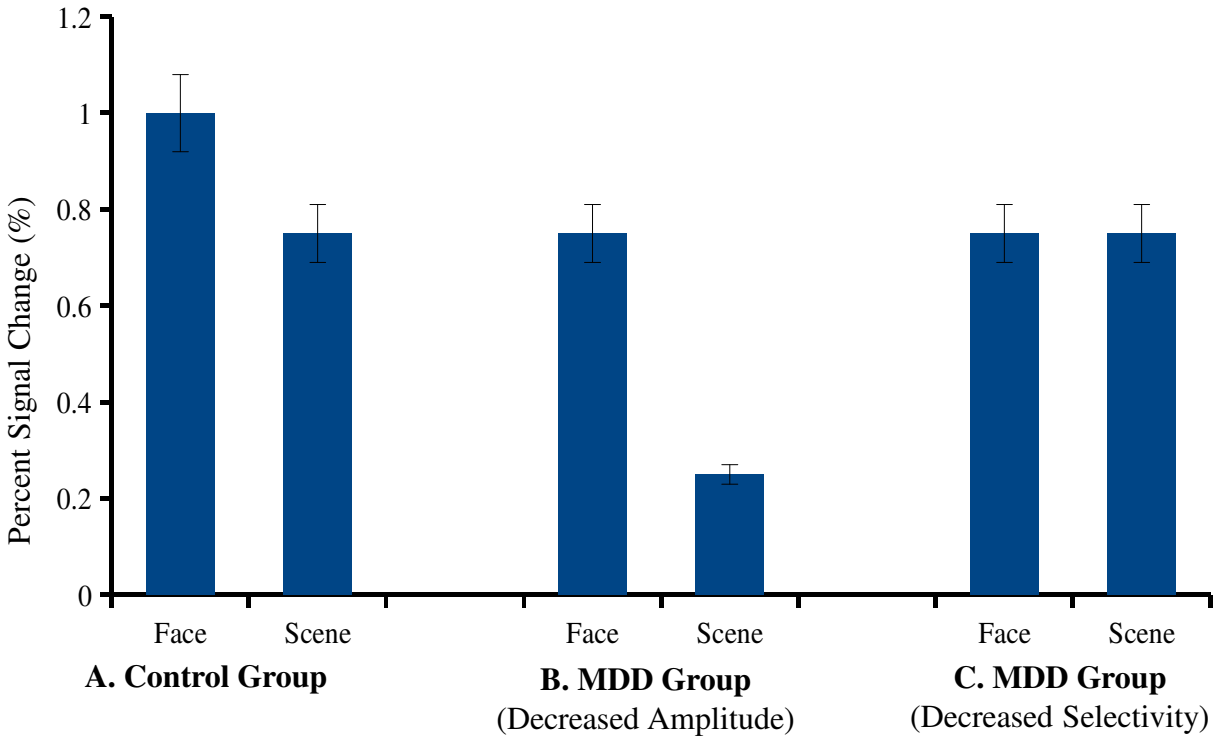
Xiao, D., & Barbas, H. (2006b). Pathways for emotions and memory II. Afferent input to the anterior thalamic nuclei from prefrontal, temporal, hypothalamic areas and the basal ganglia in the rhesus monkey. *Thalamus and Related Systems*, *2*(01), 33-28

Yonelinas, A. P., Otten, L. J., Shaw, K. N., & Rugg, M. D. (2005). Separating the brain regions involved in recollection and familiarity in recognition memory. *The Journal of neuroscience*, *25*(11), 3002–3008.

Young, K. D., Erickson, K., & Drevets, W. C. (2012). Differential effects of emotionally versus neutrally cued autobiographical memories on performance of a subsequent cognitive task: effects of task difficulty. *Frontiers in psychology*, *3*(299).

Zhong, M., Wang, X., Xiao, J., Yi, J., Zhu, X., Liao, J., Wang, W., et al. (2011). Amygdala hyperactivation and prefrontal hypoactivation in subjects with cognitive vulnerability to depression. *Biological Psychology*, *88*(23), 233–242.

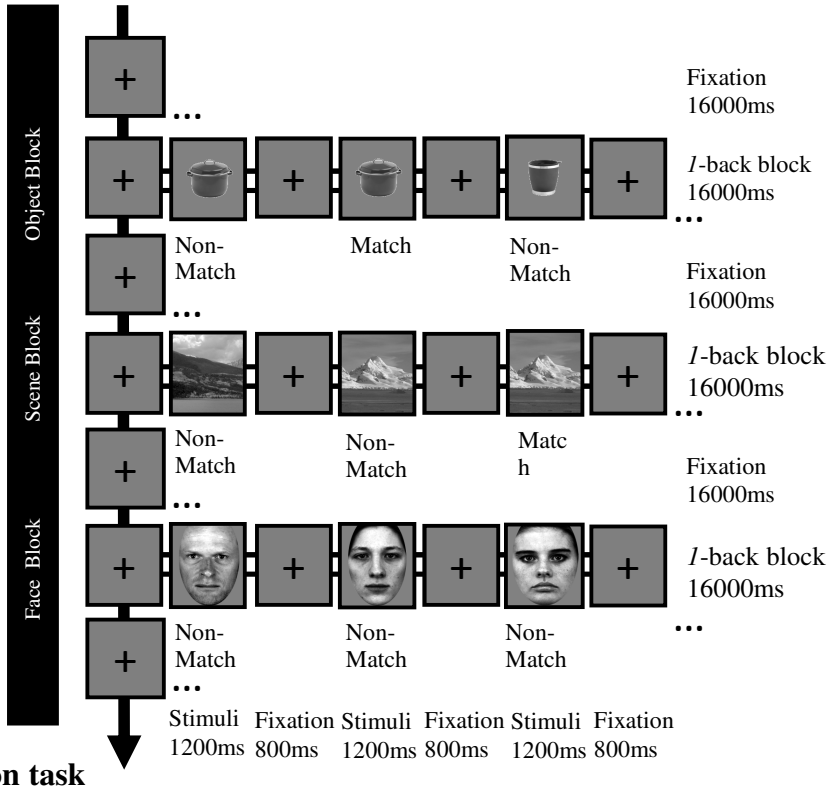
Figure 1.01



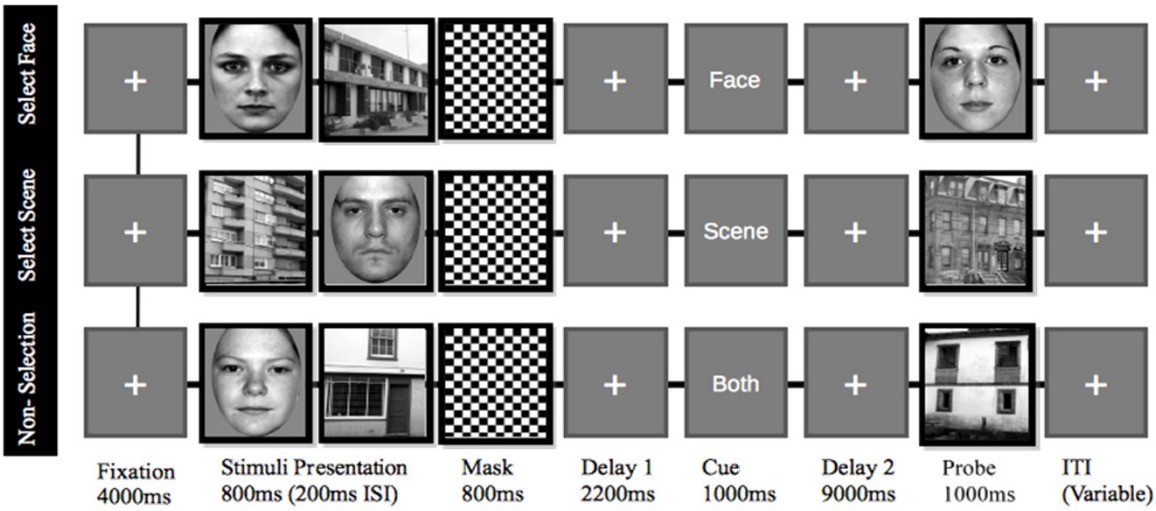
Hypothesized disruptions in MDD group subjects compared to healthy controls. In line with previous research, healthy subjects (A.) were expected to demonstrate greater response to face stimuli than to scenes in face-selective regions including the fusiform (FFA) and occipital (OFA) face areas. Disrupted activity in MDD subjects was hypothesized to take the form of (B.) decreased amplitude in these regions, (C.) decreased specificity for face stimuli in these regions, or both. The results of analyses investigating these hypotheses are shown in figures 2.03 and 2.05.

Figure 2.01

A. The functional localizer task



B. The WM selection task

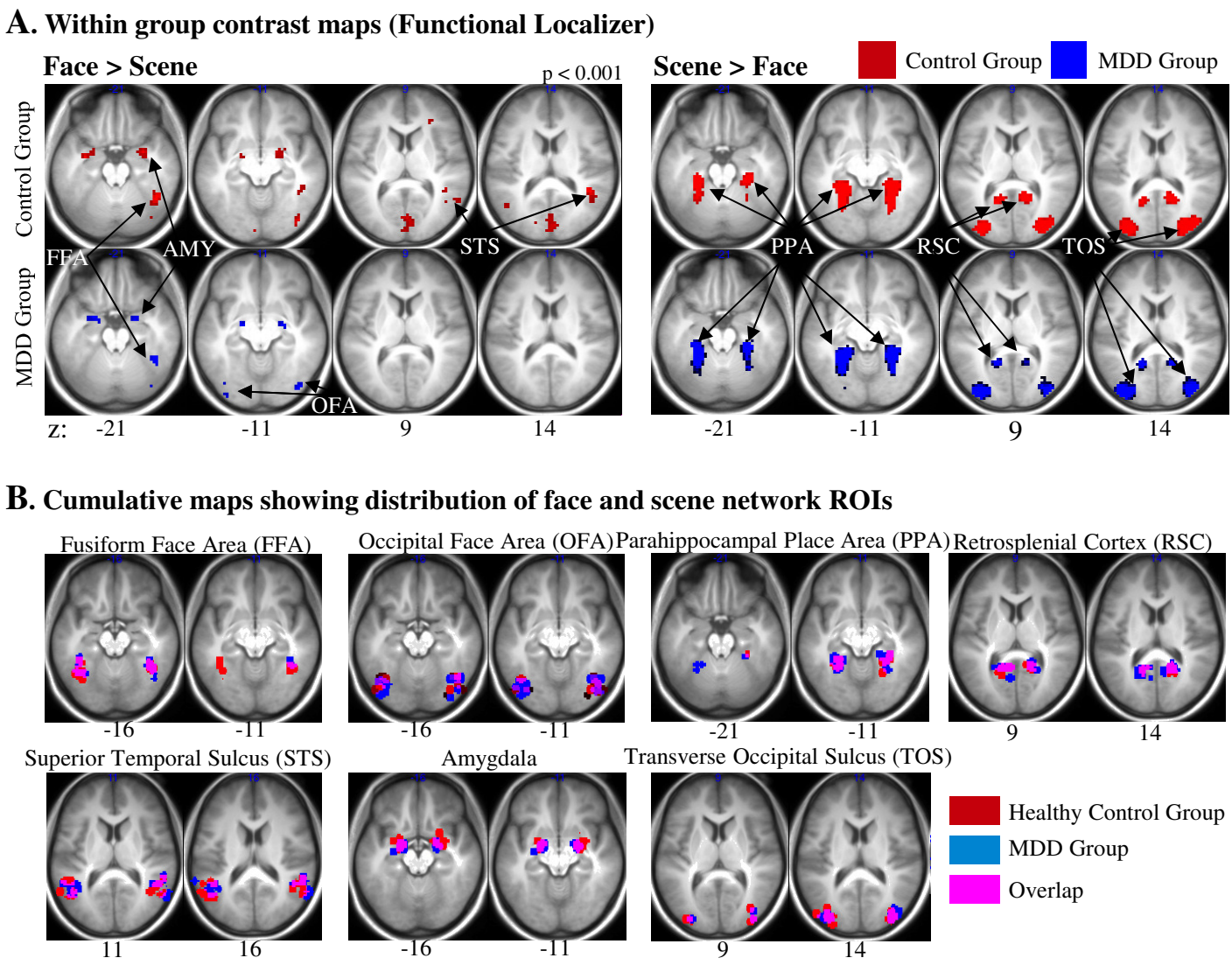


Diagrammatic representations of the functional localizer and WM selection task.

(A.) The localizer task included twelve blocks (16s in duration) in which subjects were asked to complete a 1-back task. Four blocks included face stimuli, four blocks included scene stimuli, and four blocks included object stimuli. Eight stimuli of each category were presented for 1200ms within each block (800ms ISI). No stimuli used in this task were repeated in the WM selection task or any of the post-scanning behavioral tasks. Each block was preceded and followed by fixation blocks (also 16s in duration).

(B.) Subjects completed six runs of the WM task, each consisting of 12 trials, while in the scanner. Each run contained an equal number of select-face, select-scene, and non-selection trials as well as an equal number of match and non-match probes. Trial order for the three cue conditions and two probe types were counterbalanced between and within runs.

Figure 2.02



Similar patterns of activity were observed in face and scene selective brain regions for the healthy control and MDD group subjects during the functional localizer task insofar as regions in both groups showed the expected specificity in response for their preferred visual category.

(A.) Group contrast maps showing similar face-selective and scene-selective regions brain regions in healthy control and MDD group subjects. Contrast images were drawn from comparisons of activity during face and scene blocks. Following FDR correction, clusters in the left and right STS reached statistical significance in within group contrasts for the control group only.

(B.) Maps showing the distribution of face and scene network ROIs for control and MDD group subjects. ROIs were defined based on peak coordinates derived from comparisons of face and scene block activity for each subject individually. When a subject did not show a cluster for the given ROI in face versus scene comparisons, ROIs were drawn at average coordinates from other subjects (see table 2.07). ROIs are represented by their representative size (radius 5mm). Though the location of ROIs generally did not significantly differ between groups, peak coordinates (and therefore the position of ROIs) were significantly more ventral of the parahippocampal place areas for MDD group subjects.

Figure 2.03a: Face selective ROIs

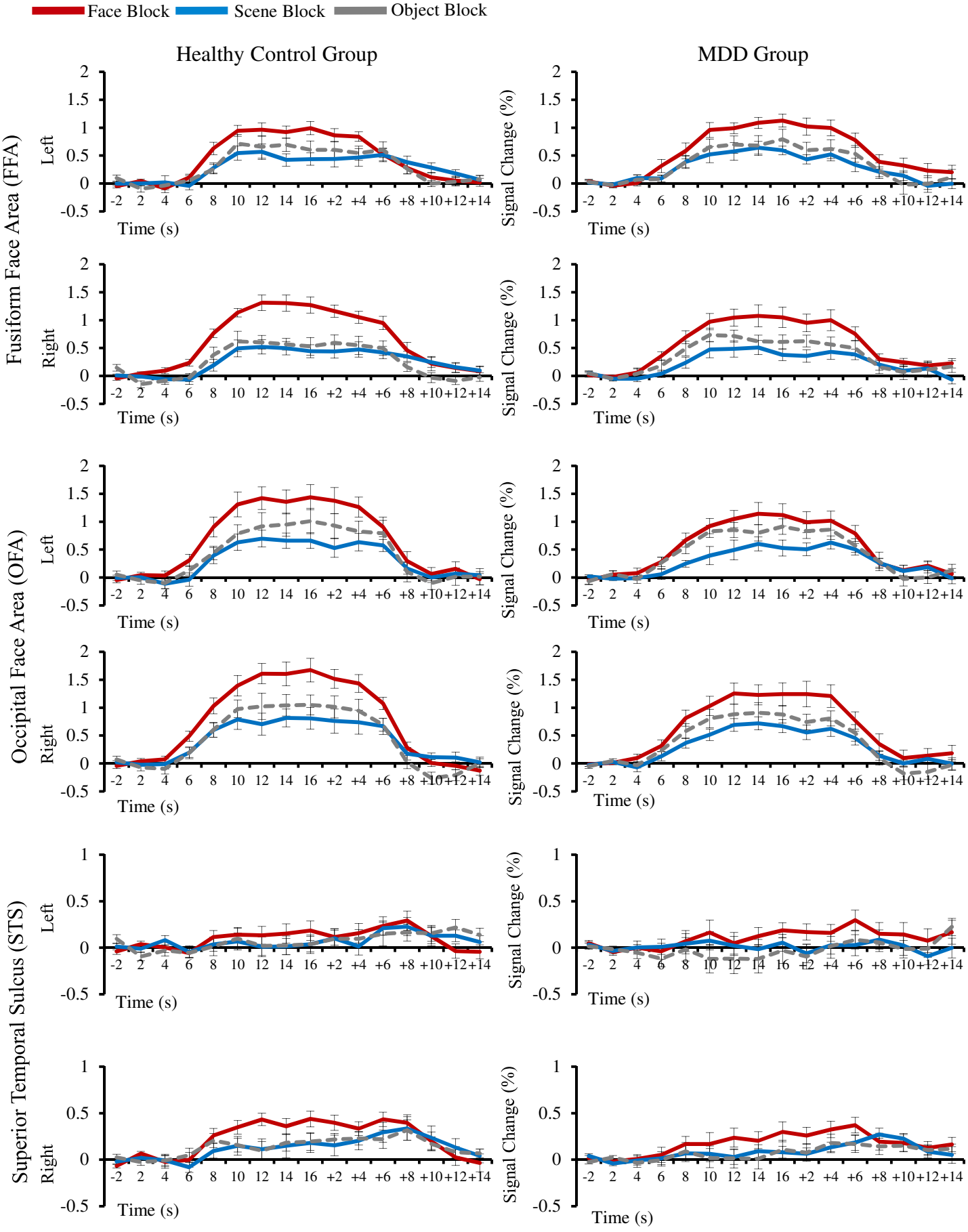


Figure 2.03b: Scene selective ROIs

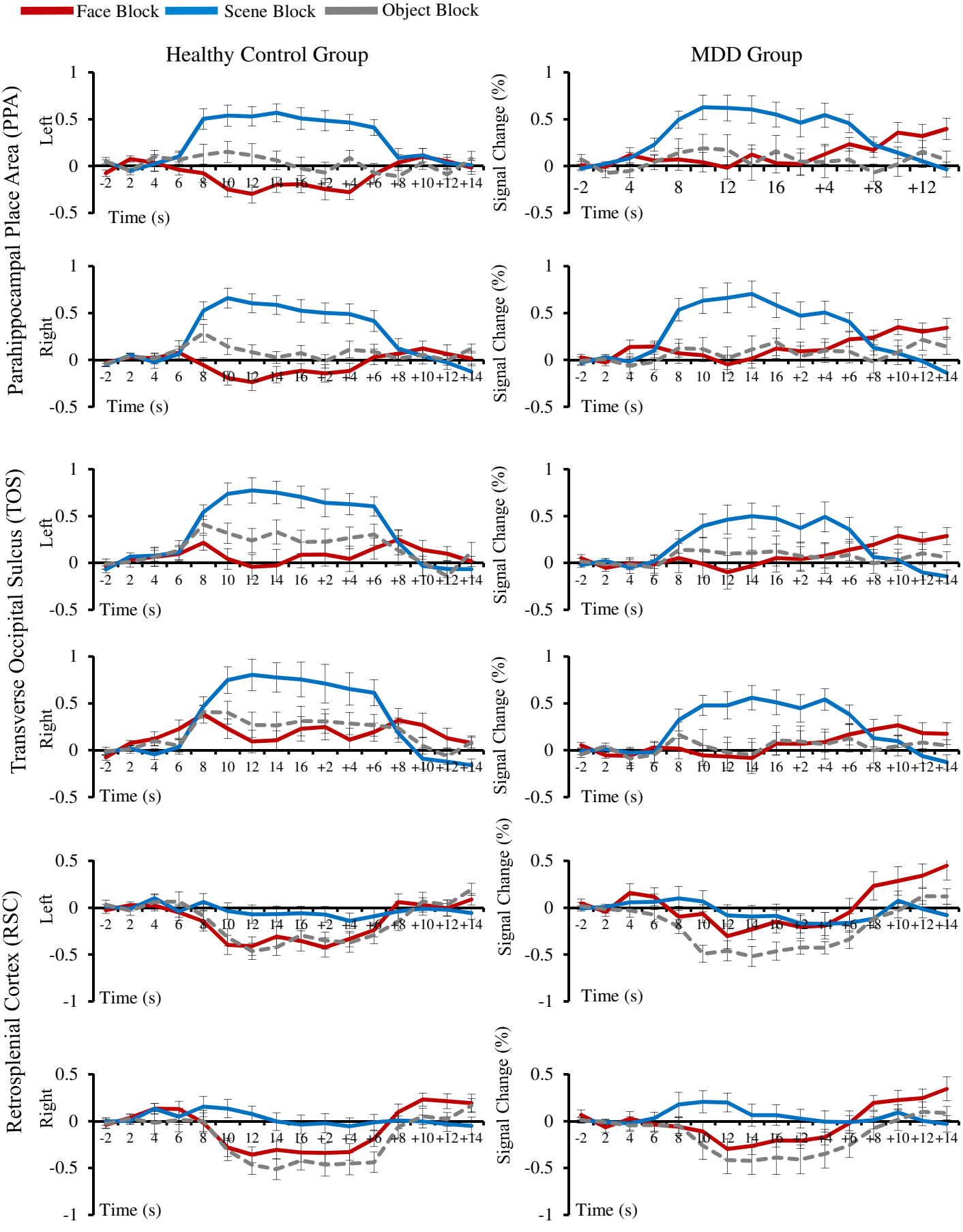
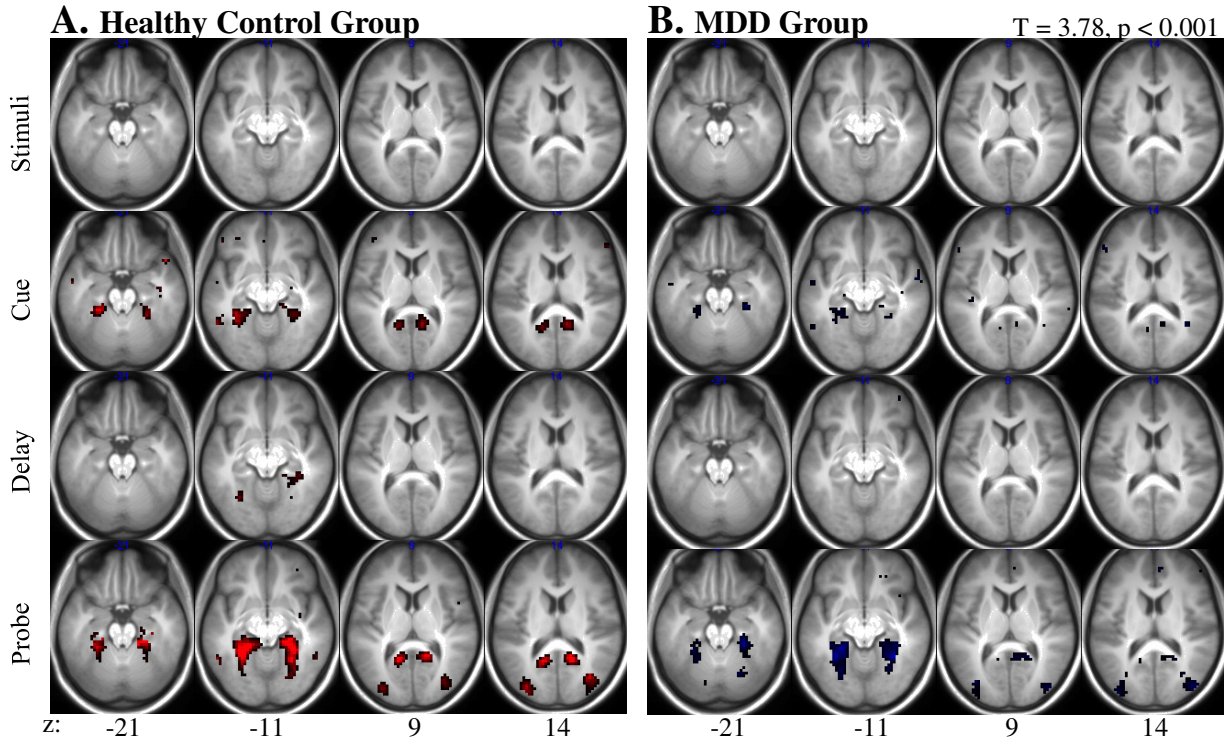


Figure 2.04



Group maps examining scene selective regions during the four study events (stimuli, cue, delay, and probe) demonstrated that the healthy control and MDD groups showed largely overlapping patterns of activity in the bilateral PPA and TOS during the cue and probe phases. During the post-cue delay period, scene-selective clusters were observed in the left and right PPA in the healthy control group only.

Corresponding comparisons examining face selective regions (Select-face > Select-scene) yielded no significant clusters during any of the four study events for either group.

Figure 2.05a: Face selective ROIs

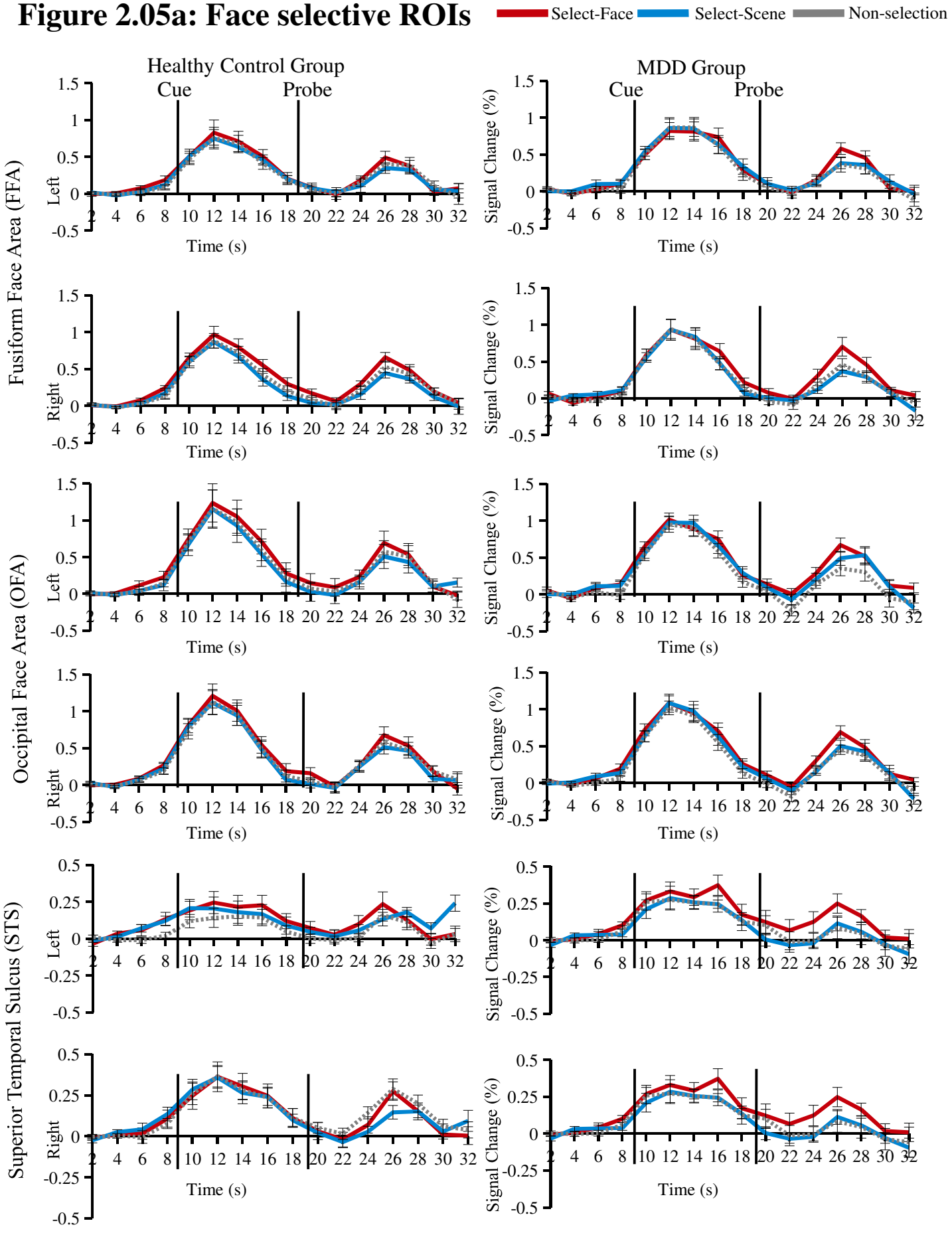


Figure 2.05b: Scene selective ROIs

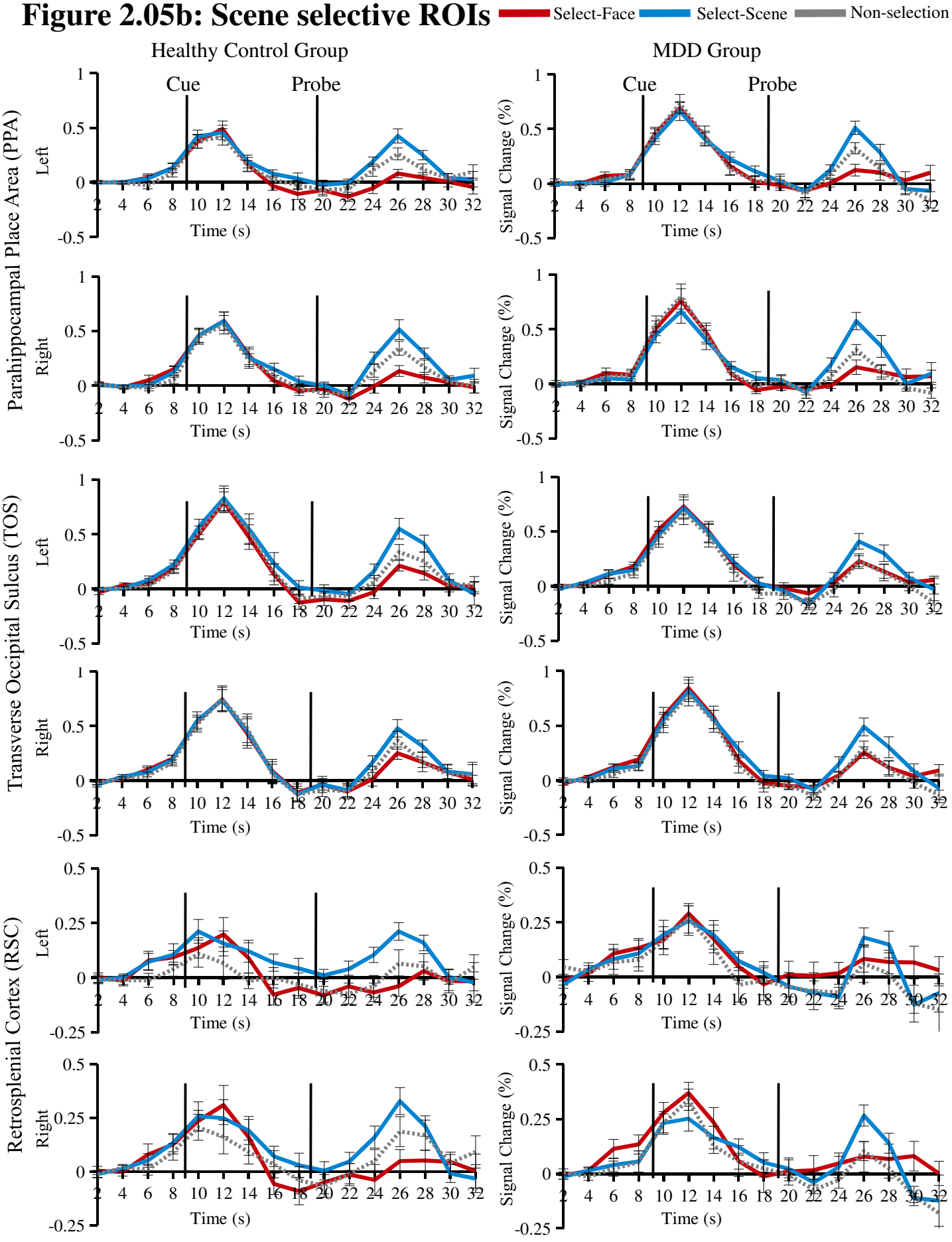


Figure 2.06: The Amygdala

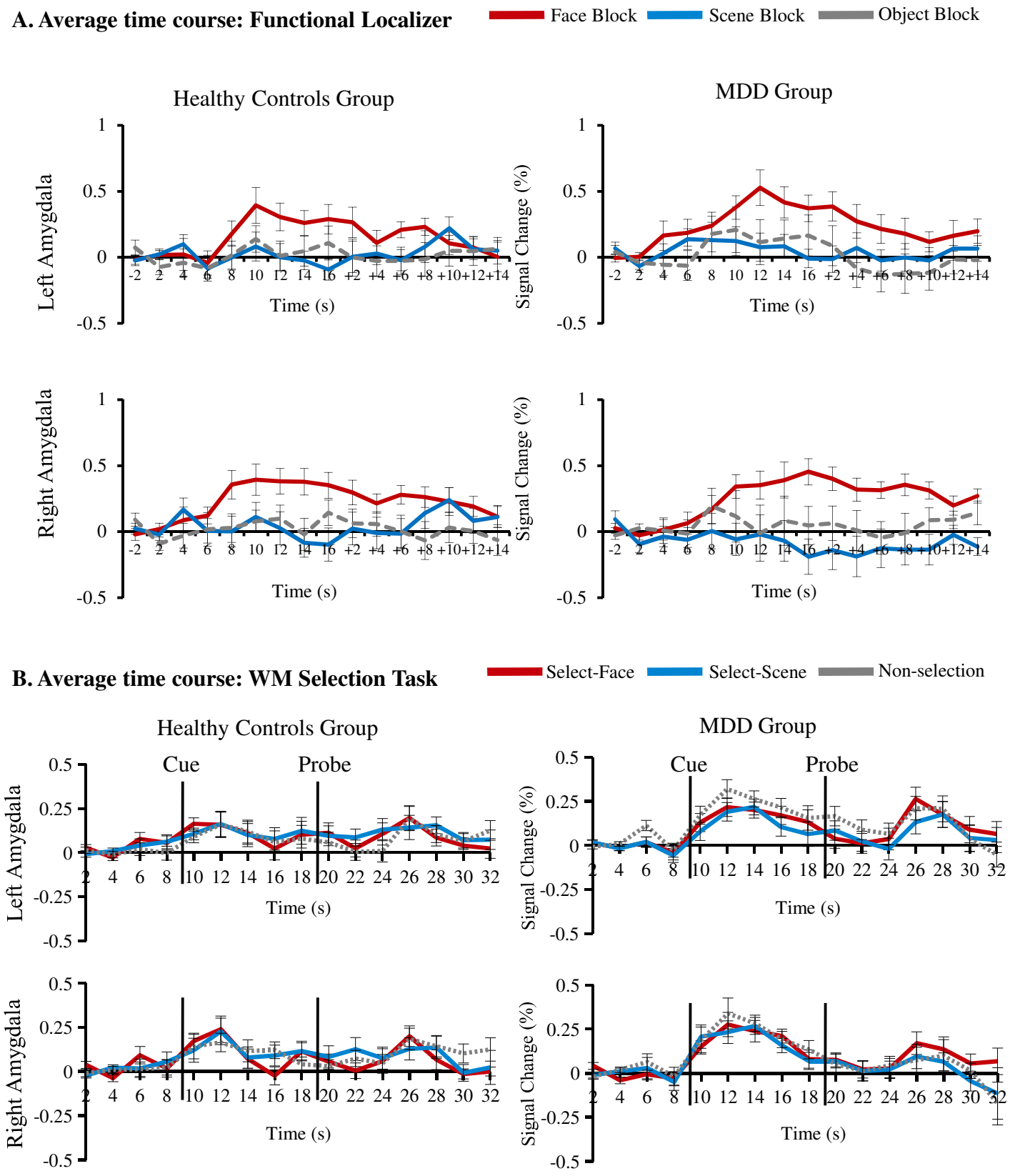
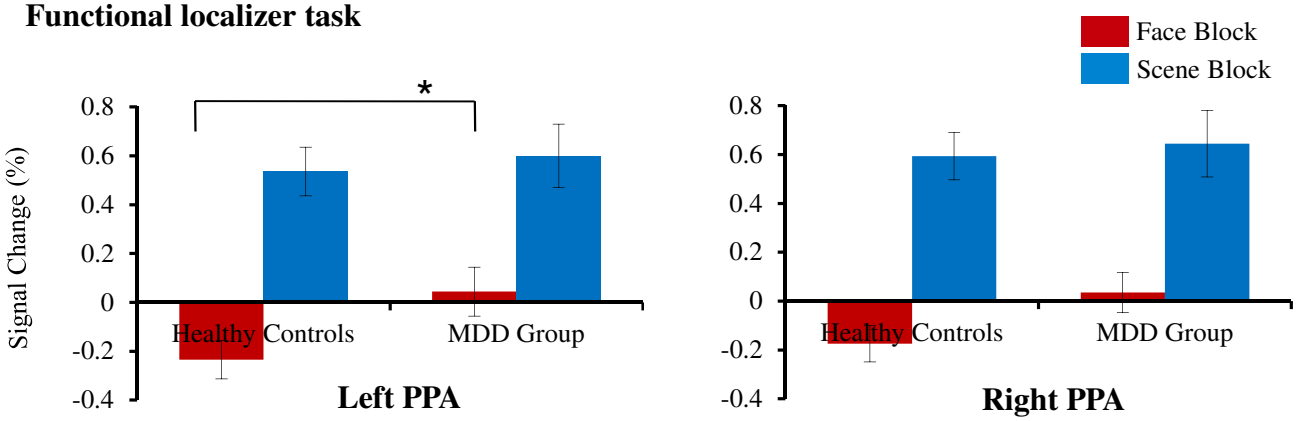
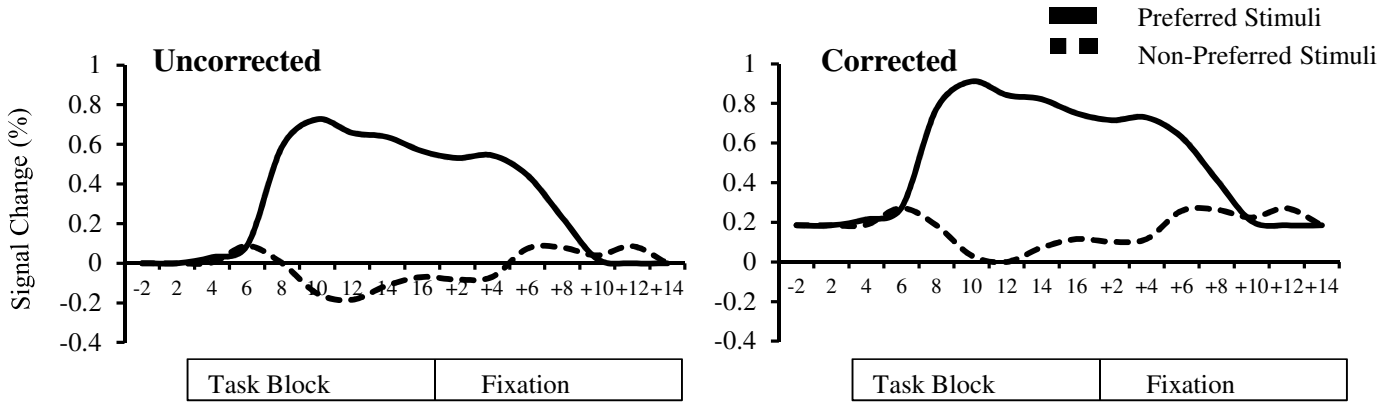


Figure 2.07

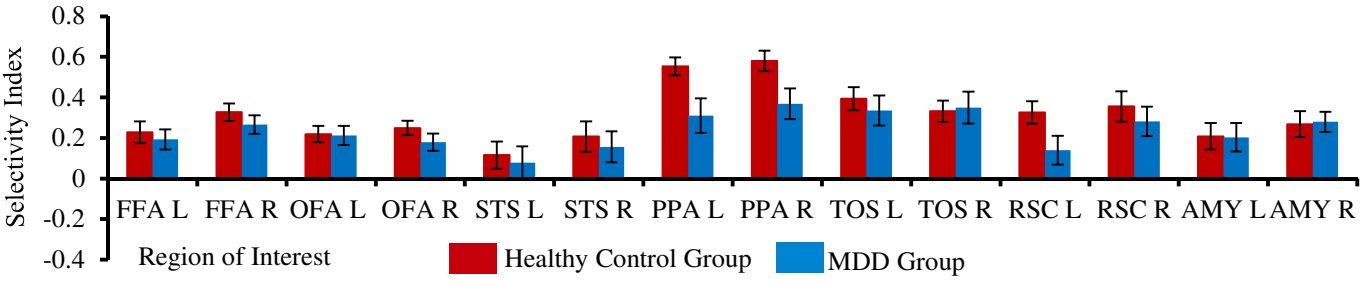
A. Specificity of the left and right PPA in healthy control and MDD group subjects: Functional localizer task



B. Demonstration of the adjustment to signal change data prior to calculation of selectivity index



C. Selectivity indices for face and scene network ROIs: Functional localizer task



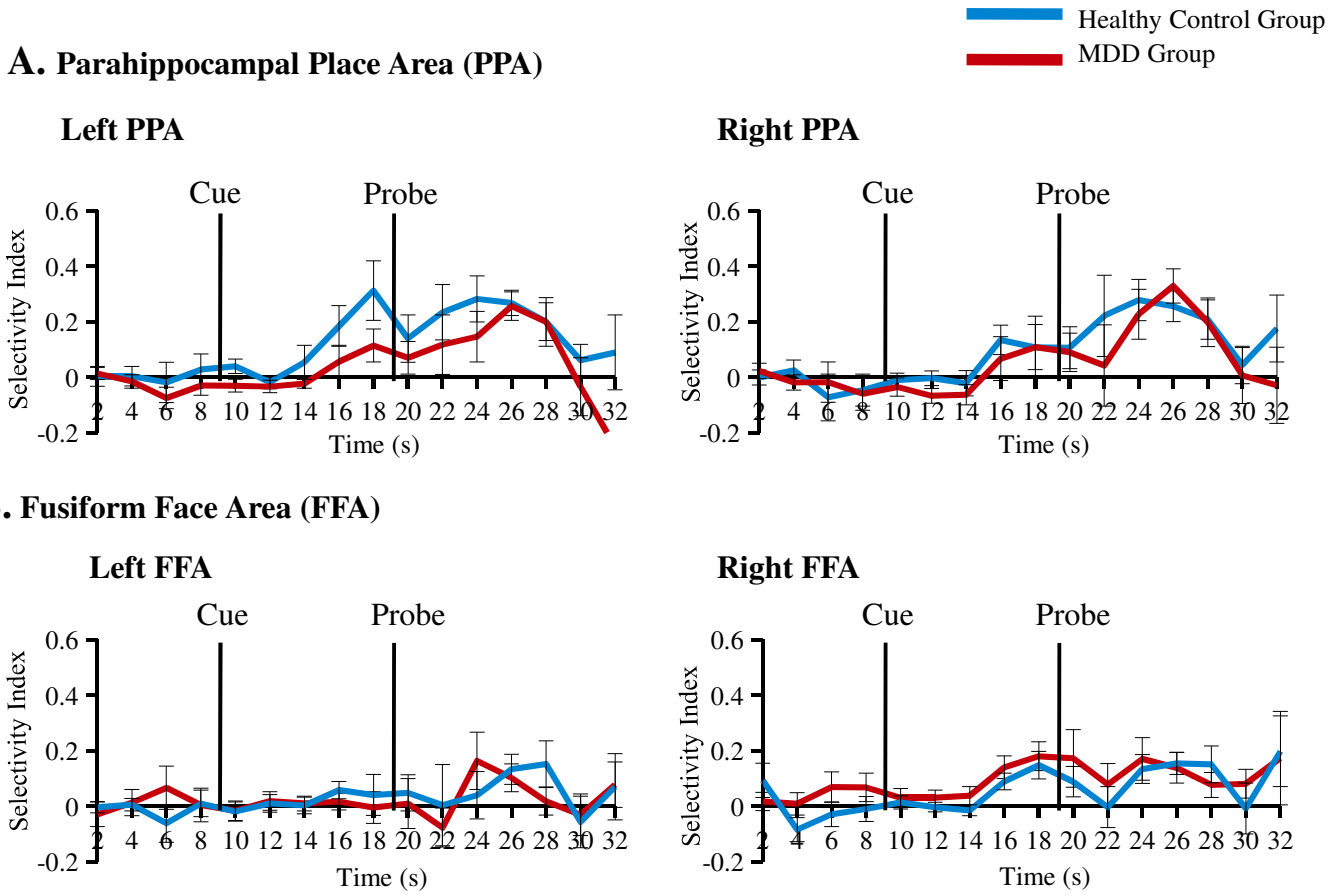
(A.) Graphical representation of average signal change in the left and right PPA during the functional localizer task for MDD and healthy control group subjects. In the left PPA, the MDD group showed significantly greater activity during face blocks than the control group. In the right PPA, increased face block activity trended towards significance.

(B.) Representation of the correction applied to percent signal change data in order to prevent inflation of selectivity indices by negative signal change values. Without correction, the selectivity index value for the example data series is greater than 3, a value clearly inflated for a scale that should be between -1 (completely selective for the non-preferred stimulus category) and 1 (completely selective for the preferred stimulus category). By comparison, the selectivity index in the corrected data series is approximately 0.79.

(C.) Graphical representation of selectivity index values for all face and scene network ROIs during the localizer task. As expected given observations of greater activity in these regions during face blocks for MDD group subjects compared to controls, significant group differences in selectivity index were observed in the left and right PPA and left RSC.

Figure 2.08

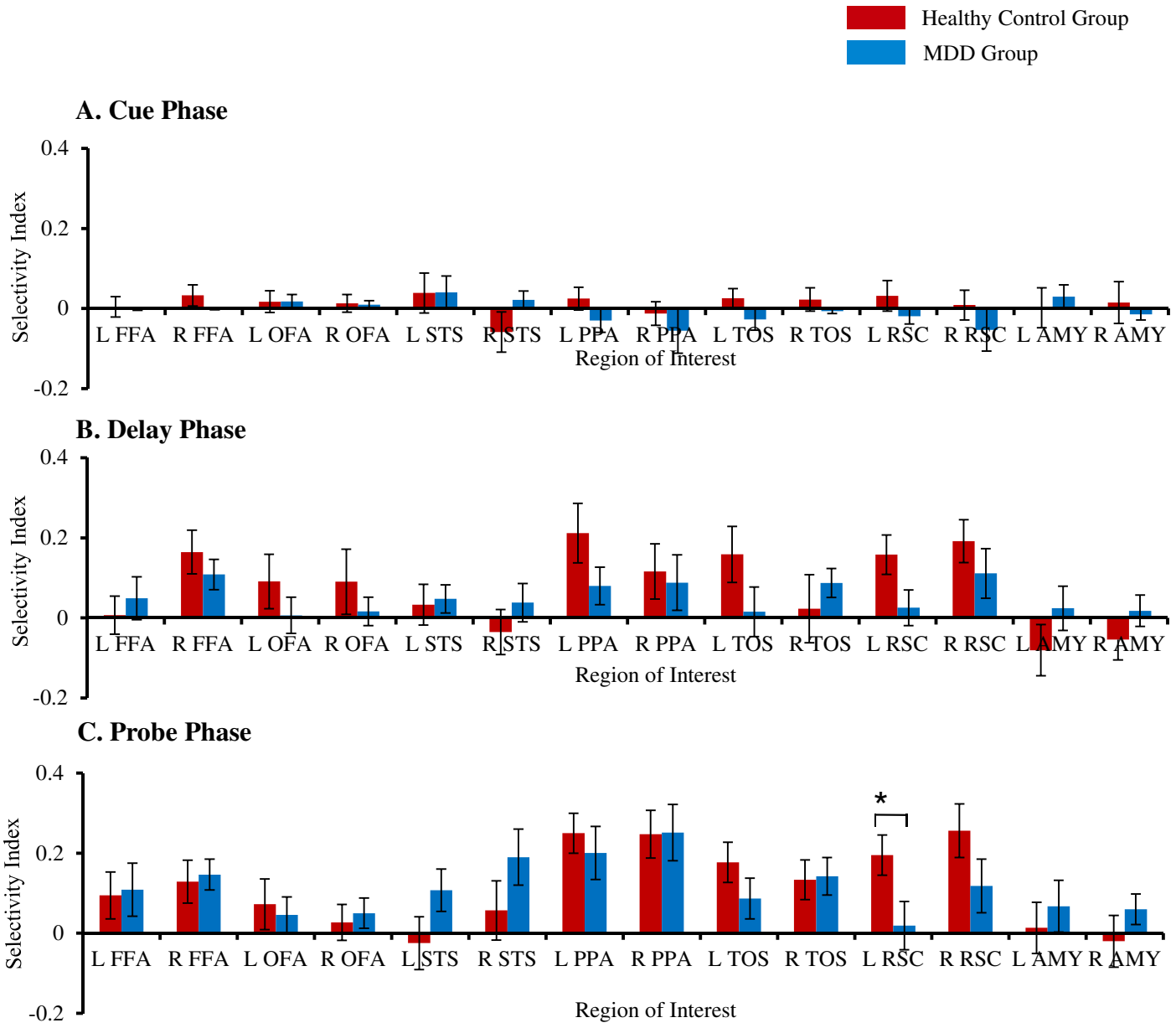
Time course of selectivity index values in the PPA and FFA during the WM selection task



Averaged time series showing change in selectivity index in the PPA and FFA during the working memory selection task demonstrated that specificity for scene stimuli in the left and right PPA increased during the post-cue delay period for both groups and peaked after the onset of the probe stimuli (A.). Fitting with data extracted within group comparisons of activity in select-face versus select-scene trials, as well as from observations of averaged time course plots (figure 2.05), selectivity was very low for both groups in regions in the face network (B.).

Figure 2.09

Selectivity index values for the face and scene network ROIs:
WM selection task



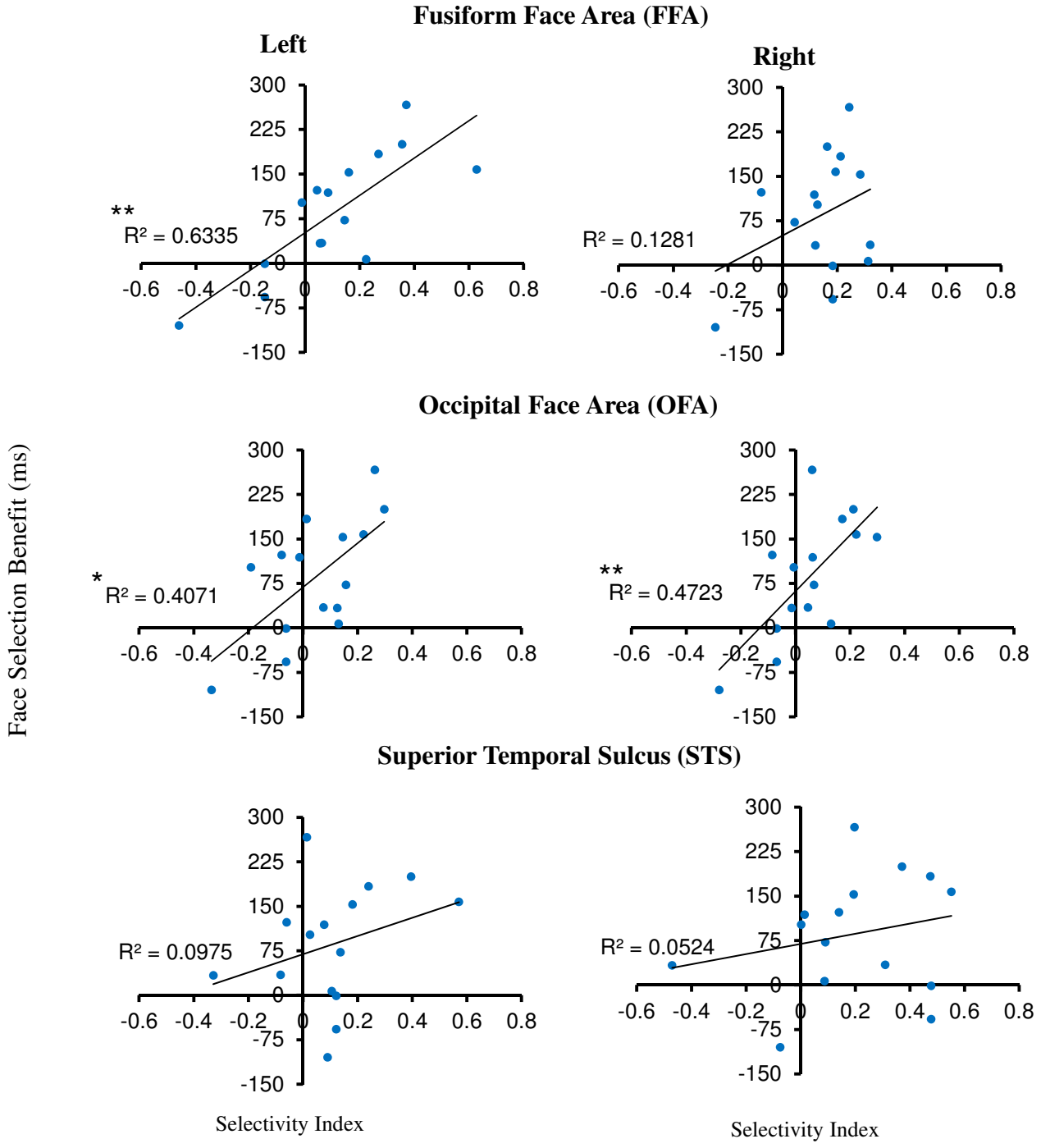
Selectivity indices for all regions of interest during the (A.) cue, (B.) delay, and (C.) probe phases of the working memory selection task.

MDD-related decreases in selectivity were significant only in the left RSC during the probe phase, with a similar decrease in this region trending towards significance during the delay period.

Though the MDD group also showed decreased selectivity in face and scene selective regions including the right FFA, left and right OFA, left PPA, and right RSC during the post-cue delay phase and right RSC during the probe phase, between group differences in these regions did not reach significance using two-tailed tests.

Figure 2.10

A. Correlations between face network selectivity and the behavioral benefit of selecting face stimuli (Probe stage)

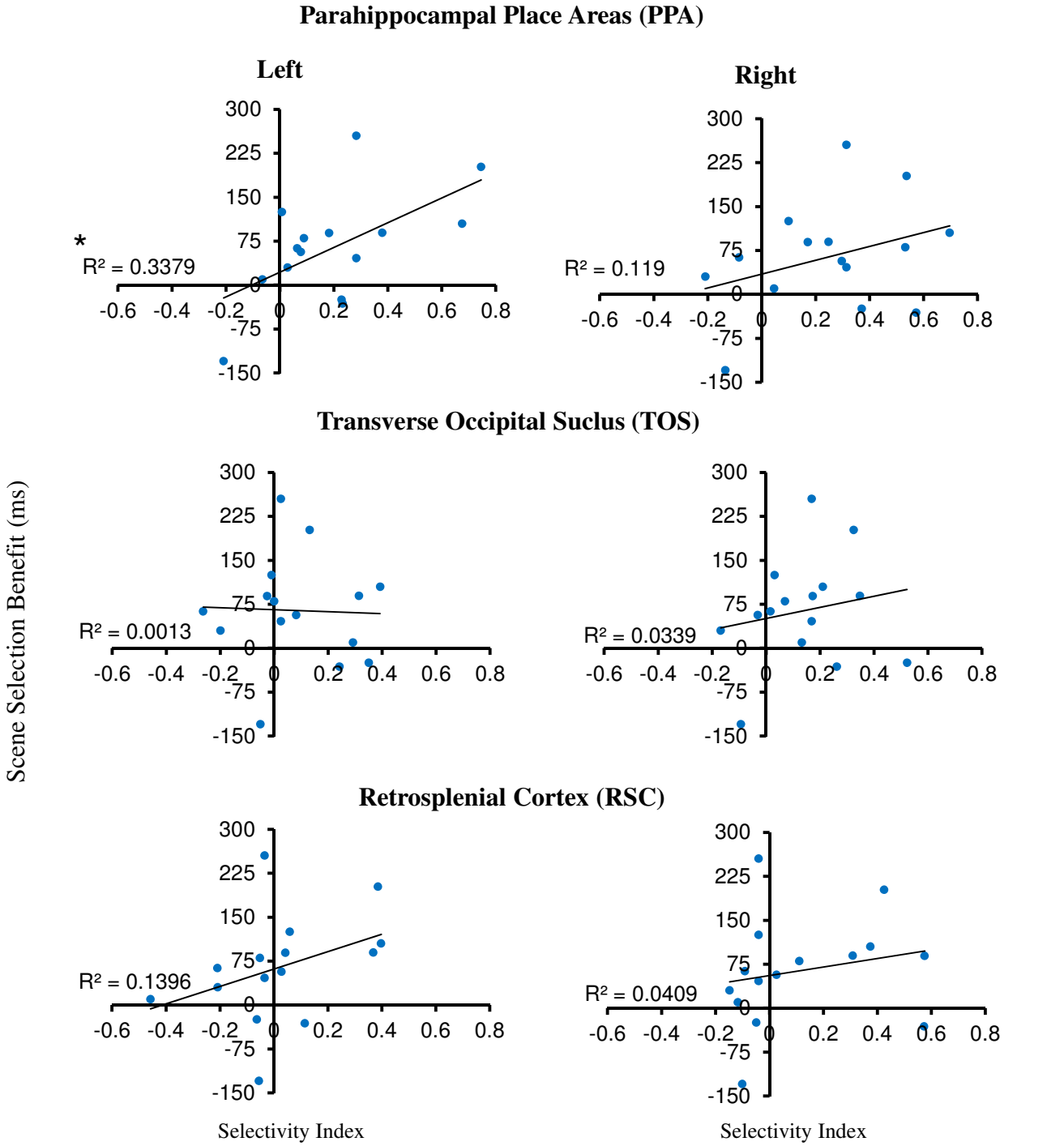


** p < 0.01
* p < 0.05

Scatter plots showing correlations between selectivity index values for face network ROIs during the probe phase of the WM selection task and the behavioral benefit of selecting face stimuli. Positive correlations were statistically significant in the left FFA, left OFA, and right OFA. Scatter plots show points for the MDD group only, similar correlations were not significant in healthy control group subjects.

Figure 2.10

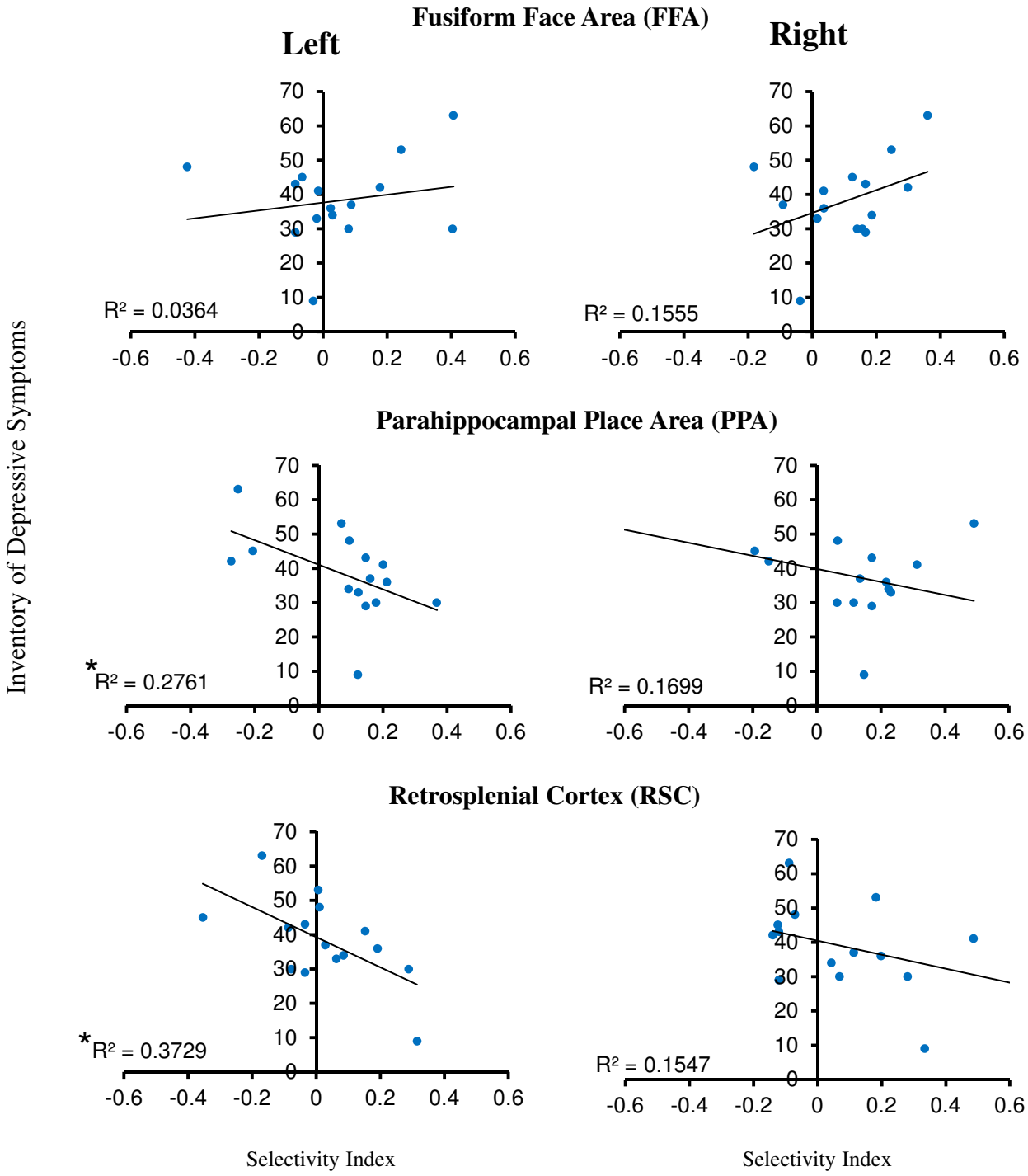
B. Correlations between scene network selectivity and the behavioral benefit of selecting scene stimuli (Probe stage)



Scatter plots showing correlations between selectivity index values for scene network ROIs during the probe phase of the WM selection task and the behavioral benefit of selecting scene stimuli. A positive correlation was statistically significant in the left PPA only. Scatter plots show points for the MDD group only, similar correlations were not significant in healthy control group subjects.

Figure 2.10

C. Correlations between selectivity index and IDS score (Delay stage)



** $p < 0.01$
* $p < 0.05$

Scatter plots showing correlations between selectivity index values for face and scene network ROIs during the delay phase of the WM selection task and IDS score A negative correlation was statistically significant in the left PPA and left RSC. Scatter plots show points for the MDD group only, similar correlations were not significant in healthy control group subjects.

Figure 3.01

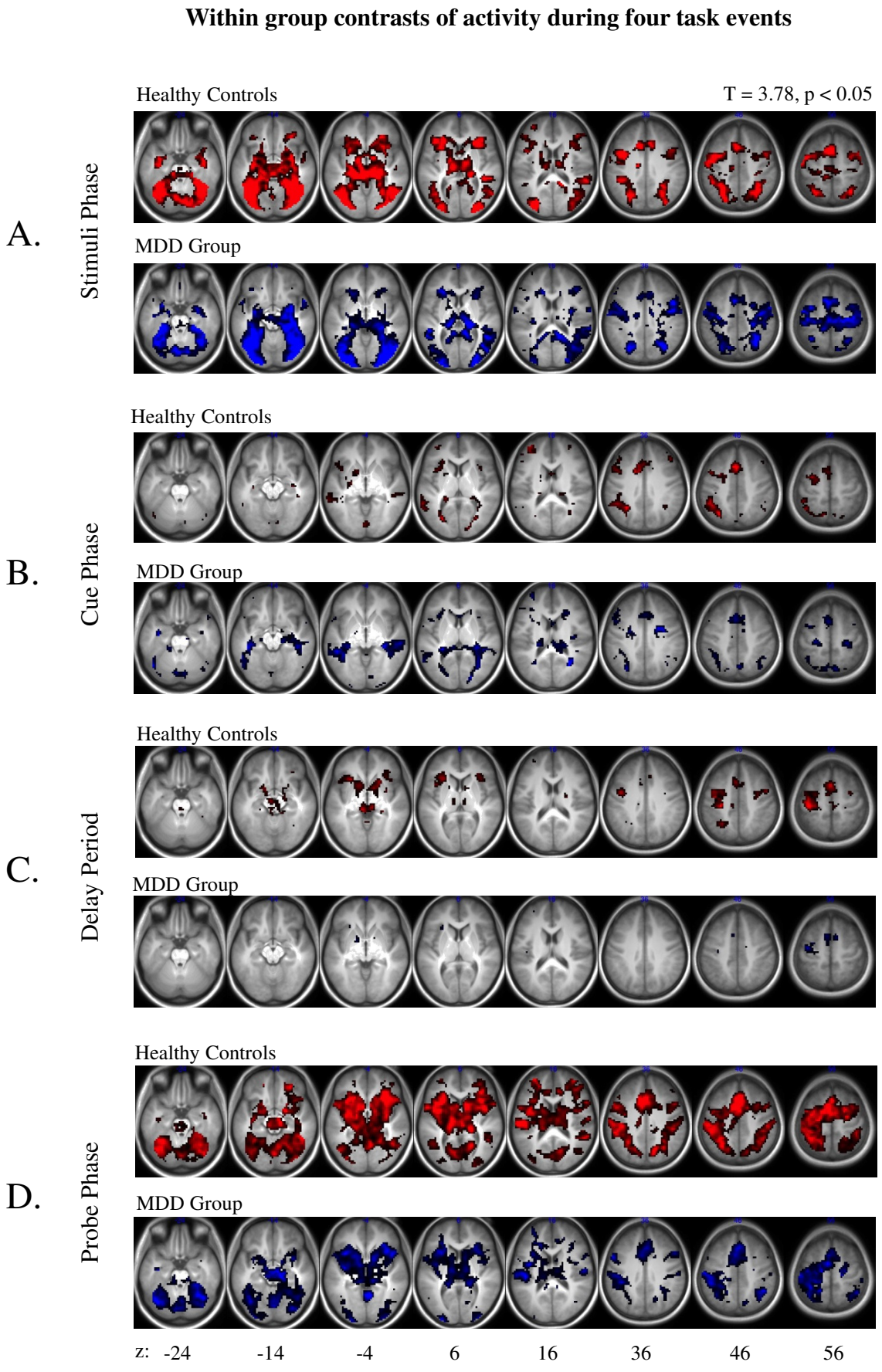
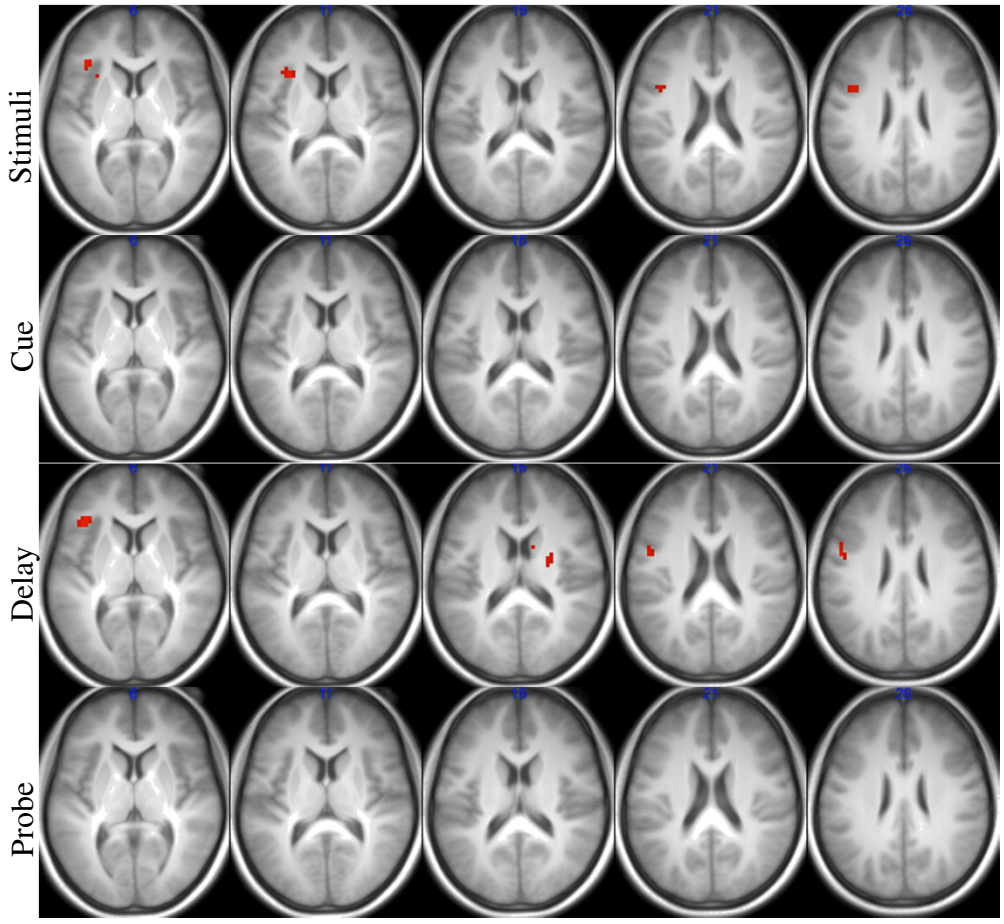

Within group contrasts of activity during four task events
Healthy Controls
T = 3.78, p < 0.05
A.
Stimuli Phase
MDD Group
Healthy Controls
B.
Cue Phase
MDD Group
Healthy Controls
C.
Delay Period
MDD Group
Healthy Controls
D.
Probe Phase
MDD Group
z: -24 -14 -4 6 16 36 46 56

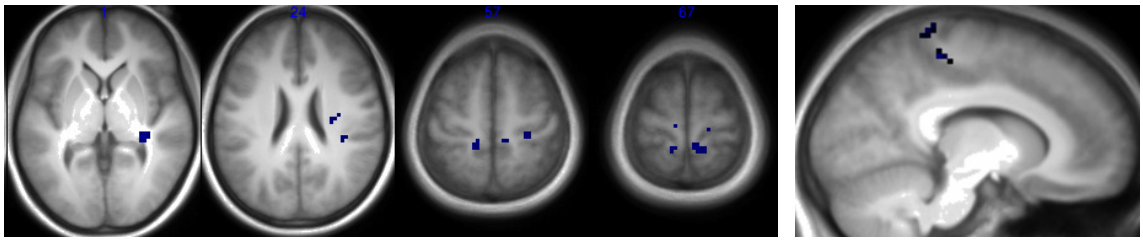
Figure 3.02

A. Results of control > MDD group comparisons of activity at the four study events



T= 3.41, p <0.05

B. Results of MDD > control group comparisons of activity during the cue phase



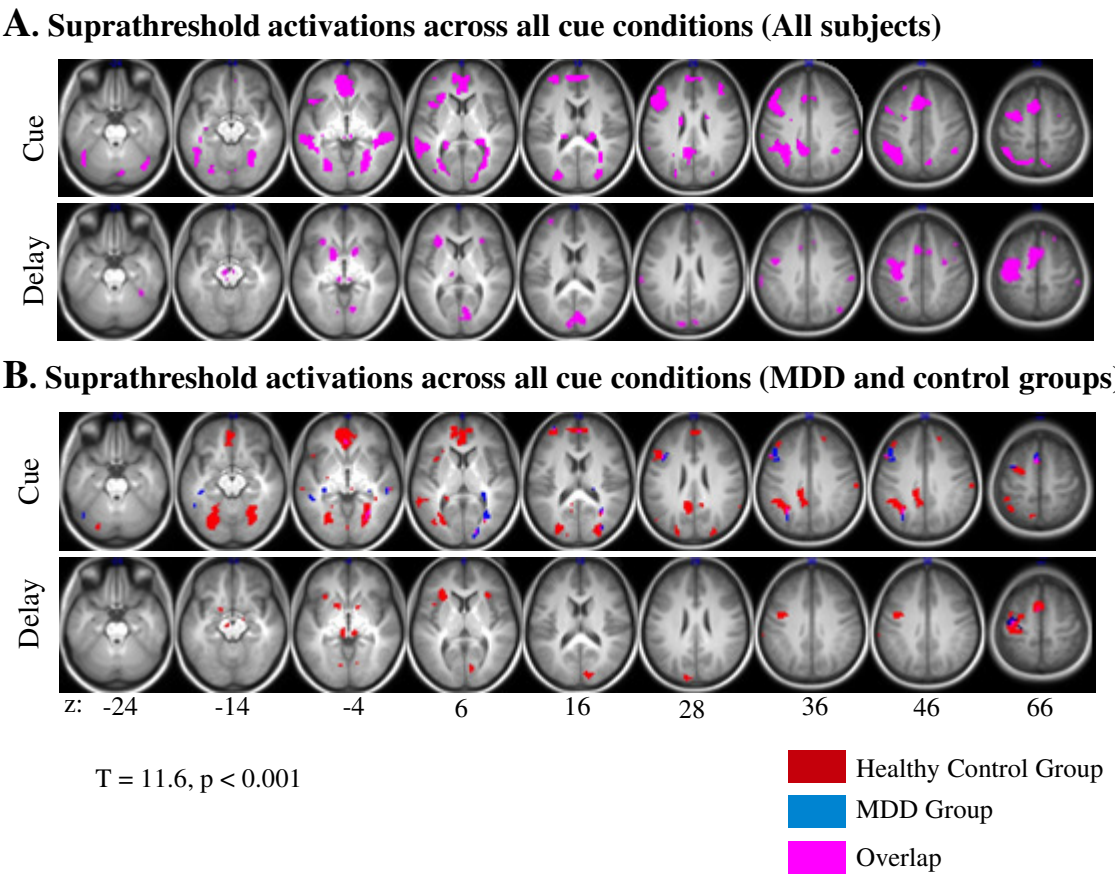
Contrast maps showing the results of group comparisons with all cue conditions pooled together.

(A.). Contrast map showing regions more active in the control group compared to MDD group during the four study phases. Following family wise error (FWE) correction, significant clusters were observed in the left ventrolateral PFC/insula.

(B.) Contrast map showing regions more active in the MDD group compared to controls during the cue phase of the working memory task with all task conditions pooled. Following FDR correction instituted at the cluster level, significant clusters were observed in the left and right somatosensory cortex.

Figure 3.03

Results of conjunction analysis showing activity across all three cue conditions



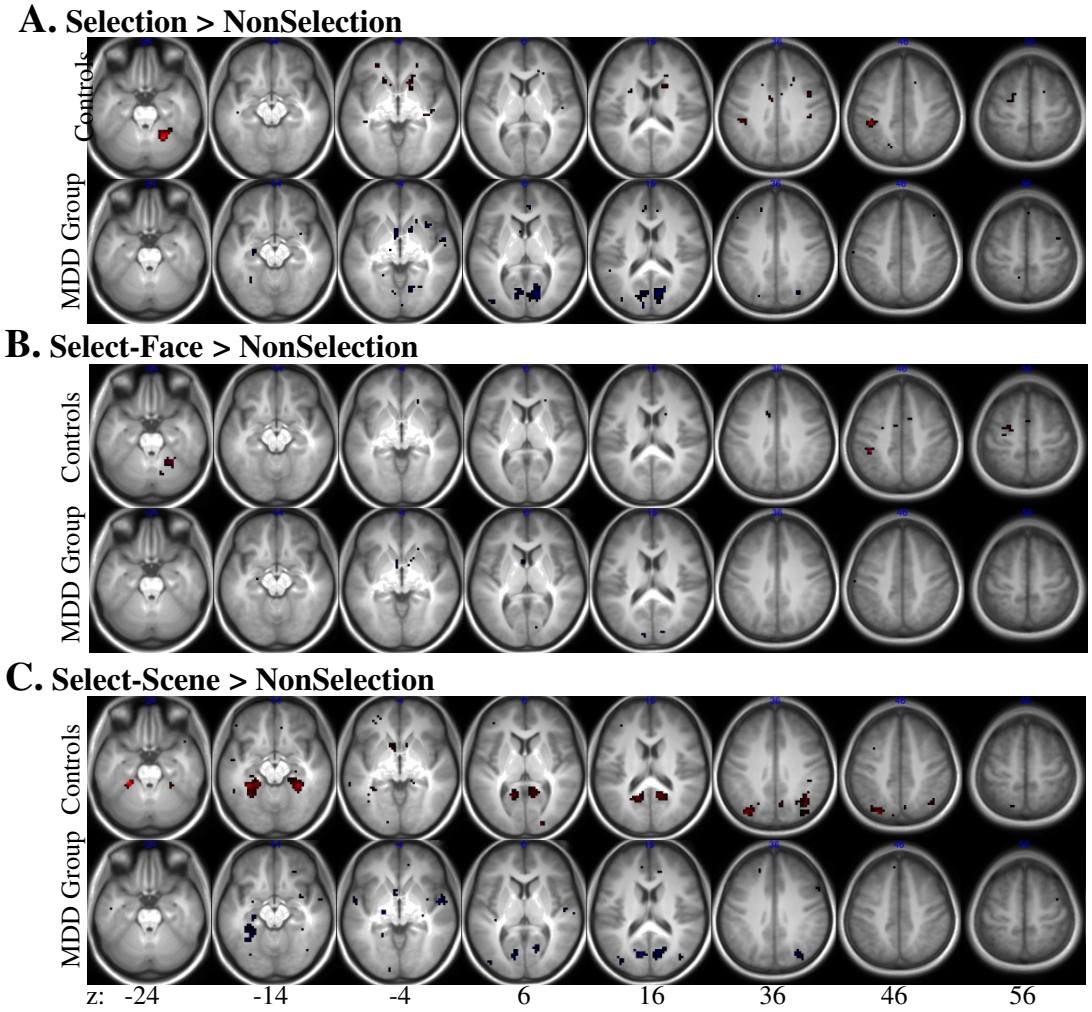
Two dimensional contrast maps showing regions active across all three cue conditions (select-face, select-scene, non-selection) during the cue and delay period.

(A.) Results of a conjunction analysis with all subjects pooled together. Significant clusters were observed in multiple frontal, parietal, and temporal lobe regions during the cue phase- including the anterior PFC, several regions within the lateral PFC, and the bilateral parahippocampal gyri. During the delay phase, with all subjects pooled together, significant clusters were observed mainly within the prefrontal cortex.

(B.) Results of conjunction analyses of healthy control and MDD group subjects separately. These analyses demonstrated the activity observed with all subjects pooled together were primarily driven by the control group. In comparison, the MDD group showed restricted activations during both phases.

Figure 3.04

Group contrast maps showing selection-related activity during the cue stage



T = 3.78, p < 0.05 (FDR Corrected at cluster level)

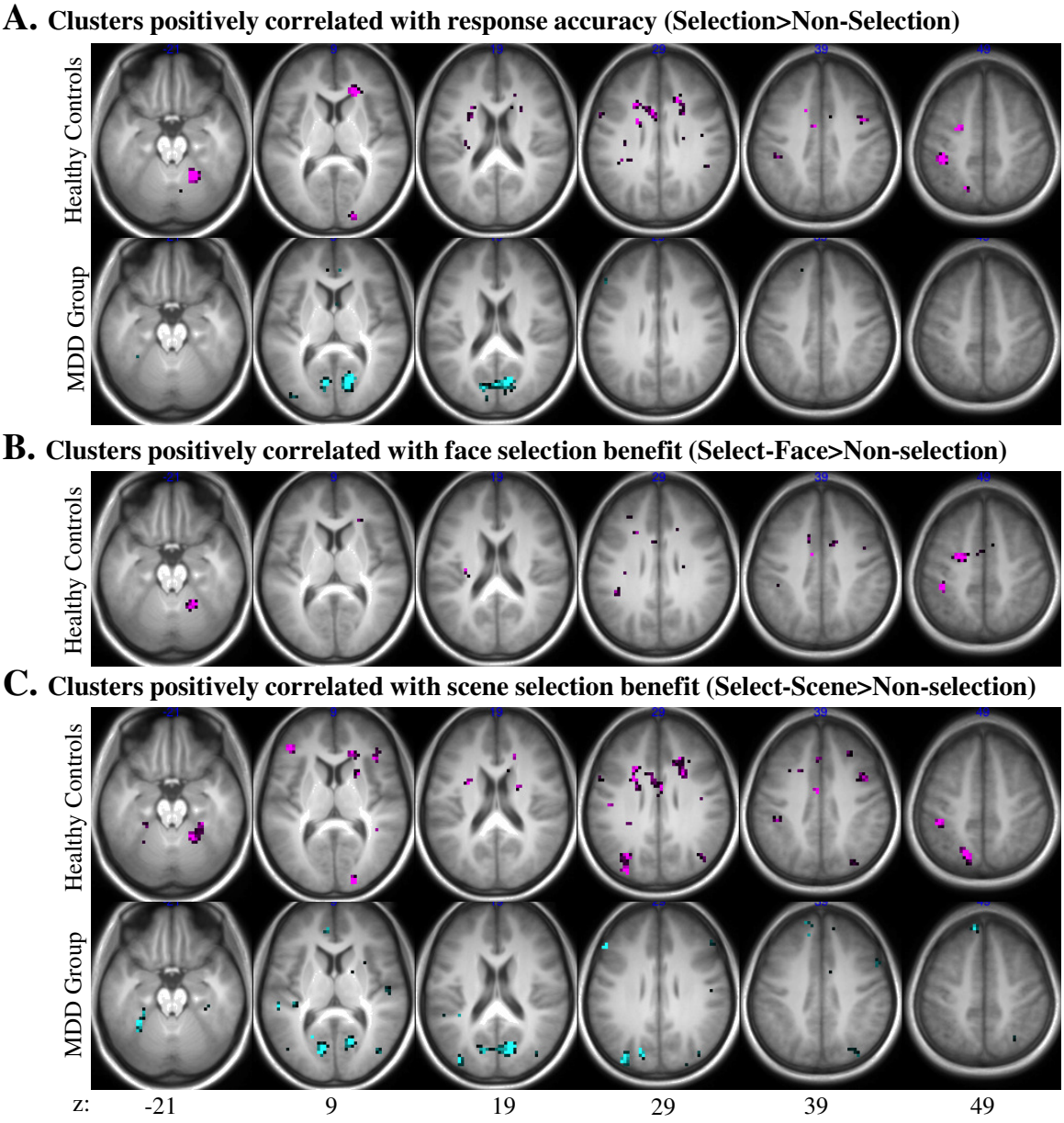
(A.) With both selection conditions pooled together (Select-face + Select+Scene), The healthy control group showed significant activity in the left IPL, cerebellum, anterior cingulate, precentral gyrus, and caudate nucleus during the cue stage. In contrast, the MDD group showed significant activity primarily in the cuneus and superior temporal gyrus

(B.) In select-face versus non-selection comparisons, only the control group showed any significant clusters after FDR correction. In select-face>non-selection contrasts, significant clusters were observed in the left IPL, precentral gyrus, and cerebellum.

(C.) In select-scene versus non-selection comparisons, the control group showed significant clusters in a number of regions including the anterior and middle cingulate, left dorsolateral PFC, caudate, putamen, cerebellum, precuneus, and middle temporal lobe during the cue phase. By comparison, the MDD group showed significant clusters mainly in the cuneus, precuneus, cerebellum, and ventral STS.

Figure 3.05

Group contrast maps showing clusters significantly correlated with measures of task performance during selection > non-selection comparisons

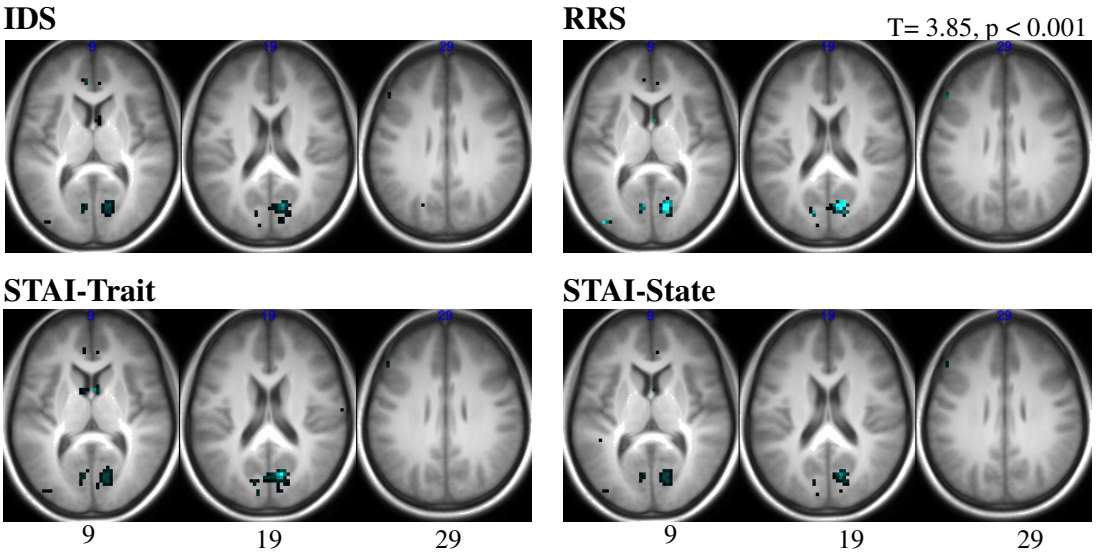


In healthy control subjects, overall response accuracy (Table 3.24) and other measures of behavioral performance positively correlated with activity in the left SPL, right parahippocampal gyrus, and left and right anterior cingulate during the cue phase in overall selection>non-selection. In the MDD group, similar correlations were significant only in the cuneus.

Figure 3.06

Group contrast maps showing clusters significantly correlated with measures of disease severity during selection > non-selection comparisons

A. Clusters positively correlated with measures of MDD symptoms severity



B. Correlation matrix showing the correlation coefficients (r) between questionnaire scores

	IDS	RRS	STAI-Trait	STAI-State
IDS	1**	0.626*	0.191	0.287
RRS	0.626*	1**	0.492+	0.296
STAI-Trait	0.347	0.492+	1**	0.730**
STAI-State	0.287	0.296	0.730**	1**

\+ $p < 0.1$ (trending)
* $p < 0.05$
** $p < 0.01$

Similar to measures of behavioral performance, scores on the IDS, RRS, and STAI (both the state and trait questionnaires) significantly correlated with overlapping clusters in the cuneus for MDD, but not the healthy control, group subjects (A.). Because such scores were significantly correlated with one another (B.) these results cannot be said to be independent.

Table 2.01
Demographic Statistics

	Healthy Controls	MDD Group
n (female)	15 (9)	15 (9)
Age	21.00 (3.34)	21.87 (3.02)
Education	2.86 (1.68)	3.2 (1.93)
Ethnicity	4 Asian, 2 Hispanic, 9 Caucasian	6 Asian, 2 Hispanic, 7 Caucasian
OSPAN	42.67 (13.84)	33.67 (19.50)
IDS	4.27 (3.84)	38.2 (12.38)***
RRS	34.53 (8.45)	63.20 (11.97)***
STAI (Trait)	32.13 (8.46)	58.6 (10.43)***
STAI (State-Pre)	35.13 (12.42)	49.87 (10.00)***
STAI (State-Post)	38.67 (10.03)	46.47 (9.03)*
Localizer ACC	83.68% (12.79%)	80.98% (13.40%)
Localizer RT	560.63ms (75.15ms)	576.52ms (49.78ms)
WM Task ACC	88.22% (7.61%)	83.81% (7.37%)
WM Task RT	1080.15ms (251.37ms)	1044.87ms (249.58ms)
Face Selection Benefit	114.27ms (101.09ms)	85.60ms (101.30ms)
Scene Selection Benefit	125.72ms (113.08ms)	64.29ms (93.02ms)
Post Memory (Overall Score)	52.46% (6.86%)	52.82% (8.22%)
Post Memory (New Faces)	53.11% (17.09.66%)	48.81% (23.41%)
Post Memory (New Scenes)	60.08% (16.55%)	59.76% (22.81%)
Valence Rating (Overall)	0.72 (0.93)	0.27 (0.93)

*** Significant at $p < 0.0001$
* Significant at $p < 0.05$

Table 2.02
Face Selective Regions from Localizer Task (Control Group)

	Name	Coordinates	Cluster Extent	T	Z
*	Right FFA	45 -52 -20	66	7.12	4.56
		45 -43 -17		5.77	4.06
*	Right STS	45 -46 13	90	6.63	4.39
		60 -58 7		5.12	3.78
		51 -55 22		4.64	3.55
*	Right Amy	30 -1 -17	61	5.99	4.15
*	Left Amy	-33 -7 -20	38	5.80	4.07
		-21 -4 -14		4.73	3.60
*	Right OFA	42 -79 -14	25	5.52	3.96
*	Cuneus	3 -88 16	57	5.33	3.87
		3 -76 10		5.03	3.74
	Precuneus	6 -61 28	18	5.27	3.85
	Cerebellum	-15 -46 -32	6	5.26	3.84
	Left OFA	-42 -82 -8	10	4.68	3.57
	Left STS	-48 -64 16	9	4.61	3.54
	Insula	27 35 7	6	4.56	3.51
		-48 -43 -11		4.17	3.30

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 2.03
Face Selective Brain Regions from Localizer Task (MDD Group)

	Name	Coordinates	Cluster Extent	T	Z
*	Right Amygdala	21 -7 -17	26	7.41	4.65
*	Right OFA	39 -79 -17	24	7.22	4.59
	Right FFA	42 -49 -20	16	6.75	4.43
*	Left Amygdala	-21 -4 -17	37	6.69	4.41

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 2.04
Scene Selective Brain Regions from Localizer Task (Control Group)

	Name	Coordinates	Cluster Extent	T	Z
*	Left PPA	-27 -46 -11	300	15.10	6.23
		-27 -61 -11		10.73	5.50
*	Right TOS	36 -88 19	352	12.02	5.75
		33 -82 13		11.84	5.71
		30 -73 31		5.97	4.14
*	Left TOS	-33 -82 25	347	10.29	5.40
		-30 -85 13		10.29	5.40
		-27 -88 31		7.48	4.67
*	Right PPA	30 -43 -5	296	8.54	4.98
		30 -28 -17		7.85	4.79
		24 -55 -11		7.31	4.62
*	Right RSC	15 -52 13	81	7.63	4.72
*	Left RSC	-15 -55 10	48	6.63	4.39
	Left SPL	-21 -67 46	10	5.24	3.83

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 2.05
Scene Selective Brain Regions from Localizer Task (MDD Group)

	Name	Coordinates	Cluster Extent	T	Z
*	Right PPA	30 -46 -11	281	10.52	5.45
		27 -61 -11		6.89	4.48
*	Left PPA	-21 -46 -14	355	9.24	5.16
		-30 -49 -5		8.55	4.98
		-30 -40 -17		7.96	4.82
*	Left TOS	-36 -85 13	297	9.07	5.12
		-42 -82 19		8.86	5.06
		-27 -85 10		7.78	4.76
*	Right TOS/SPL	42 -85 16	516	6.59	4.38
		18 -52 16		6.52	4.35
		39 -76 19		6.47	4.33
*	Left RSC	-15 -55 13	57	6.23	4.24
*	Left DMPFC	-9 26 43	9	5.59	3.99
*	Right SPL	-15 -79 46	68	5.07	3.76
		-21 -64 46		5.07	3.76
		-24 -67 34		4.14	3.29

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 2.06
Between Groups Analysis
Healthy Controls>MDD Group: Face Blocks

	roi	Coordinates	Cluster Extent	T	Z
*	Left superior frontal gyrus	-27 5 37	97	5.52	4.50
		-39 -4 37		4.69	3.99
		-48 -1 46		4.41	3.81
	Cingulate	18 5 40	10	5.03	4.21
	Left SPL	-30 -46 55	28	4.89	4.13
	Left PHG	-30 -55 4	7	4.27	3.71
	Precuneus	-18 -61 58	19	4.16	3.64
		-24 -58 49		3.76	3.36
	Precuneus	-15 -46 58	6	3.85	3.42
	Claustrum	-33 -1 10	10	3.82	3.40

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 2.07
Average ROI coordinates

ROI	x	y	z	Control Group	MDD Group
Left FFA	-40.5	-50.97	-20.09	14	14
Right FFA	41.82	-49.53	-19.82	15	15
Left OFA	-40.59	-70	-14	15	13
Right OFA	42.94	-69.72	-11.38	14	14
Left STS	-51.94	-52.84	11.41	14	14
Right STS	53.72	-50.78	11.59	14	14
*Left PPA	-26.45	-47.36	-10.64	15	14
*Right PPA	28.32	-43.88	-10.21	15	15
Left TOS	-35	-85.64	15.82	15	14
Right TOS	38.63	-82.47	15.06	15	13
Left RSC	-15.21	-55.93	11.55	13	12
Right RSC	17.52	-54.52	14.74	14	13
Left Amygdala	-19.55	-6.69	-14.93	12	14
Right Amygdala	22.29	-5.29	-15.29	11	13

Table 2.08
Scene Selective Brain Regions: Cue Phase (Control Group)

	Name	Coordinates	Cluster Extent	T	Z
*	Left PPA	-24 -37 -23	157	8.50	4.97
		-33 -43 -8		7.17	4.57
		-30 -28 -17		4.53	3.49
	Right Anterior Temporal	48 17 -20	6	7.54	4.69
	Cuneus	21 -91 4	13	7.32	4.62
*	Right PPA	30 -40 -14	231	7.15	4.57
		12 -52 10		6.64	4.39
		12 -37 1		5.39	3.90
*	Left TOS	-33 -76 31	160	7.12	4.56
		-36 -76 40		6.66	4.40
		-27 -76 46		6.14	4.21
*	Right SPL	36 -55 31	144	6.99	4.51
		39 -61 40		5.74	4.05
		39 -79 31		5.69	4.03
	Precuneus	6 -64 40	20	6.51	4.35
	Left LOT	-54 -52 -11	19	6.10	4.19
		-48 -43 -11		4.17	3.30
*	Left RSC	-15 -55 10	92	5.97	4.14
		-21 -58 16		5.14	3.79
	Left Anterior Temporal	-54 -7 -20	9	5.36	3.89
	Left Amygdala	-6 8 -5	15	4.73	3.60
	PCC	3 -37 22	13	4.52	3.49
		-3 -34 31		4.43	3.44
	Right Amygdala	9 14 -5	6	4.39	3.43
	VLPFC	-33 41 -8	8	4.37	3.41

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 2.09
Scene Selective Brain Regions: Cue Phase (MDD Group)

	Name	Coordinates	Cluster Extent	T	Z
	Insula	42 -19 -8	6	7.08	4.55
	Right PPA	30 -34 -20	34	6.06	4.18
		27 -46 -11		4.36	3.41
		21 -34 -14		4.14	3.29
*	Left PPA	-21 -37 -17	115	5.54	3.97
		-30 -49 -14		5.39	3.90
		-24 -43 -5		5.06	3.75
	Precentral sulcus	0 -28 73	17	5.41	3.91
		3 -16 73		4.49	3.47
*	Anterior temporal (right)	57 -4 -8	41	5.39	3.90
	Right TOS	33 -85 28	17	5.21	3.82
		33 -76 34		3.83	3.11
	Anterior Temporal (Left)	-57 -10 -8	24	5.04	3.75
		-48 -10 -23		4.48	3.47
	White Matter (FOF)	36 -55 13	7	4.96	3.71
	Right ITS	60 -40 -5	8	4.90	3.68
	Left DLPFC	-51 29 13	8	4.77	3.62

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 2.09
Scene Selective Brain Regions: Cue Phase (MDD Group)
(Continued)

Name	Coordinates	Cluster Extent	T	Z
Insula	-39 -28 7	6	4.76	3.61
	-33 -19 -2	22	4.76	3.61
	-33 -10 -5		4.38	3.42
Premotor Cortex	48 -1 22	8	4.71	3.59
	51 8 22		4.08	3.25
Thalamus	-21 -7 1	6	4.37	3.41
	-36 -22 28	8	4.13	3.29
	-42 -13 22		4.01	3.22
Left RSC	-6 -61 13	13	4.07	3.25
	-9 -55 4		3.96	3.19
	9 -55 13	9	4.03	3.23

Table 2.10
Scene Selective Brain Regions: Delay Phase (Control Group)

	Name	Coordinates	Cluster Extent	T	Z
*	Somatosensory Cortex	18 -37 70	50	6.30	4.27
		18 -31 52		5.72	4.04
		24 -25 64		4.60	3.53
*	Left PPA (Post)	-27 -58 -8	26	5.78	4.07
*	Right PPA	36 -37 -14	50	5.78	4.07
		18 -37 -11		4.72	3.59
		24 -49 -11		4.11	3.27
	Left PPA (Ant)	-24 -43 -5	7	4.56	3.51
	Left TOS	-30 -76 19	6	4.44	3.45

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 2.11
Scene Selective Brain Regions: Probe Phase (Control Group)

	Name	Coordinates	Cluster Extent	T	Z
*	Left PPA	-30 -46 -11	512	15.65	6.30
		-21 -40 -11		13.07	5.93
		-27 -40 -17		11.00	5.55
*	Right PPA	18 -37 -17	1126	13.79	6.04
		27 -31 -17		12.21	5.78
		18 -55 16		11.79	5.70
*	Left TOS	-33 -82 31	419	10.62	5.47
		-30 -76 37		9.13	5.13
		-21 -73 46		8.38	4.94
*	Left LOT Cortex	-54 -55 -8	40	7.18	4.58
*	Right IPS	48 -43 40	68	6.69	4.41
	Right DLPFC	30 29 37	15	5.64	4.01
	Middle ACC	18 -1 34	8	5.21	3.82
	Left Thalamus	-12 -22 16	11	5.16	3.80
		-3 -16 19		4.42	3.44
	Right LOT Cortex	54 -52 -11	8	5.08	3.77
	Somatosensory Cortex	9 -40 49	9	5.04	3.74
	Right IPS	-42 -43 40	9	4.96	3.71
	Right STS	24 11 52	12	4.65	3.56
	Posterior Left PPA	-24 -85 -14	8	4.48	3.47
	Left SFS	-24 5 52	8	4.21	3.33
		-21 8 43		4.13	3.28

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 2.12
Scene Selective Brain Regions: Probe Phase (MDD Group)

	Name	Coordinates	Cluster Extent	T	Z
*	Right PPA	33 -49 -11	296	7.02	4.52
		27 -34 -20		6.44	4.32
		36 -37 -14		5.71	4.04
*	Left PPA	-30 -49 -14	285	6.87	4.47
		-24 -40 -11		6.72	4.42
		-24 -55 -14		5.67	4.02
*	Right TOS	33 -85 28	524	6.62	4.39
		39 -67 22		6.51	4.35
		18 -73 46		6.18	4.22
*	Cerebellum	9 -82 -35	46	6.55	4.36
		33 -67 -44		5.01	3.73
		24 -70 -38		4.65	3.56
*	Left TOS	-36 -76 7	120	5.89	4.11
		-39 -88 16		5.44	3.92
		-33 -76 19		4.86	3.66
*	APFC	9 47 25	46	4.96	3.71
		6 47 13		4.72	3.59
		9 41 37		4.40	3.43

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 2.12
Scene Selective Brain Regions: Probe Phase (MDD Group)
(Continued)

Name	Coordinates	Cluster Extent	T	Z
DLPFC	33 14 55	7	4.61	3.54
Cerebellum	-27 -70 -47	6	4.55	3.51
VMPFC	30 38 -5	7	4.53	3.50
Thalamus	-12 -7 4	10	4.43	3.44
VLPFC	48 50 -5	6	4.39	3.43
Right RSC	-21 -61 31	18	4.33	3.39
	-12 -49 7		4.09	3.26
	-15 -55 16		3.90	3.15

Table 3.01
Within Groups Analysis
WM Selection Task: Stimuli Phase (Controls)

	Name	Coordinates	Cluster Extent	T	Z
*	Cerebellum	36 -64 -14	15845	22.94	7.06
		-33 -82 -8		19.95	6.79
		-21 -31 -2		19.42	6.74
*	Middle Frontal Gyrus	-33 50 19	35	6.42	4.31
	Precentral Gyrus	66 -7 25	13	5.87	4.10
	Superior Temporal Gyrus	51 -19 -2	9	5.34	3.88
	Insula	-42 -31 19	7	5.08	3.76
	Caudate	24 -31 25	8	5.05	3.75
	Claustrum	-36 -7 10	6	4.87	3.66
	Caudate	18 -19 28	8	4.77	3.62
	Insula	36 -25 25	11	4.35	3.40

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.02
WM Selection Task: Cue Phase (Healthy Controls)

	Name	Coordinates	Cluster Extent	T	Z
*	Cingulate gyrus	-3 17 46	921	10.71	5.49
		-9 20 40		8.00	4.83
		-15 8 37		7.42	4.65
*	Posterior Cingulate	-27 -73 4	298	10.31	5.41
		-60 -43 4		6.74	4.43
		-45 -46 1		5.80	4.08
*	SPL	-30 -64 46	517	9.65	5.26
		-30 -55 40		9.23	5.16
		-48 -46 43		7.22	4.59
*	Superior Frontal gyrus	-33 50 19	98	8.52	4.98
		-48 38 19		4.96	3.71
		27 -73 4	325	7.55	4.69
*	Cuneus	21 -82 4		6.16	4.22
		21 -31 13		6.03	4.17
*	Middle Frontal Gyrus	39 44 28	74	7.54	4.69
		45 32 34		5.84	4.09
		45 26 43		5.84	4.09
	Lentiform nucleus	33 -16 -11	17	6.52	4.35
*	Cerebellum	45 -67 -26	85	5.90	4.12
		39 -55 -32		5.80	4.08
*	Thalamus	-21 -37 7	29	5.89	4.11
		-21 -28 16		4.52	3.49
	Cerebellum	-15 -37 -26	9	5.88	4.11
*	Lentiform nucleus	-15 8 -2	63	5.85	4.10
		-18 2 13		4.31	3.38
		-24 2 4		4.24	3.35
*	Claustrum	-27 26 4	131	5.58	3.98
		-36 11 7		5.27	3.85
		-42 14 -8		4.77	3.62

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.02
WM Selection Task: Cue Phase (Healthy Control)
(Continued)

Name	Coordinates	Cluster Extent	T	Z
Claustrum	-24 -10 -5	33	5.55	3.97
	-33 -19 -14		5.41	3.91
Cerebellum	-45 -58 -29	39	4.98	3.71
	-42 -67 -26		4.85	3.65
	-48 -61 -20		4.53	3.49
Caudate	0 5 16	6	4.93	3.69
Supramarginal gyrus	63 -52 25	17	4.89	3.67
Middle Frontal Gyrus	30 50 19	17	4.88	3.67
Cerebellum	-33 -61 -50	13	4.88	3.67
Supramarginal gyrus	36 -49 37	34	4.85	3.65
	48 -58 46		4.24	3.35
Insula	39 14 7	12	4.68	3.57
	33 20 7		4.24	3.35
Cerebellum	15 -67 -38	8	4.68	3.57
Precuneus	9 -67 52	27	4.54	3.50
Precuneus	21 -67 58	6	4.45	3.46

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.03
WM Selection Task: Delay Phase (Control Group)

	Name	Coordinates	Cluster Extent	T	Z
*	Superior Frontal gyrus	-30 53 22	21777	16.54	6.42
		0 17 49		15.55	6.29
		-54 -25 19		14.90	6.20
	Middle Frontal Gyrus	-18 44 -14	21	6.69	4.41
		-27 44 -2		3.90	3.16

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.03
WM Selection Task: Probe Phase (Healthy Controls)

	Name	Coordinates	Cluster Extent	T	Z
*	Insula	-42 -1 40	955	8.81	5.05
		-39 -25 52		8.47	4.96
		-30 -25 46		8.00	4.83
*	Insula	-36 23 4	1242	8.32	4.92
		9 -25 1		7.71	4.74
		-6 -31 -2		7.46	4.67
*	Putamen	33 -1 -8	11	7.51	4.68
*	Superior Parietal Lobule	-27 -55 46	98	6.13	4.21
*	Precentral Gyrus	48 -1 46	113	6.04	4.17
		33 -4 52		5.63	4.00
*	Precentral Gyrus	15 -28 73	145	5.96	4.14
		6 -28 58		5.17	3.80
		0 -19 61		5.13	3.79
	Cingulate gyrus	-3 2 28	76	5.80	4.08
		-9 17 31		5.47	3.94
		6 2 28		4.67	3.57
		24 -10 16	11	5.16	3.80
	Medial Frontal Gyrus	9 26 37	7	4.68	3.57
	Fusiform Gyrus	-30 -46 -17	11	4.50	3.48
	Inferior Frontal Gyrus	42 5 31	11	4.34	3.40

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.05
WM Selection Task: Stimuli Phase (MDD Group)

	Name	Coordinates	Cluster Extent	T	Z
*	Parahippocampal gyrus	27 -34 -14	15799	20.95	6.89
		-30 -97 4		20.65	6.86
		24 -94 -8		18.34	6.62
*	Superior Temporal Gyrus	-48 -40 7	110	11.14	5.58
		-51 -49 4		7.88	4.79
		-51 -28 1		4.60	3.53
*	Superior Temporal Gyrus	54 11 -14	52	8.05	4.84
	Anterior Cingulate	21 32 25	9	5.71	4.04
*	Cerebellum	3 -52 -32	81	5.41	3.91
		12 -46 -44		5.14	3.79
		21 -37 -41		4.57	3.51
	Cerebellum	-12 -46 -44	13	5.36	3.89
	Anterior Cingulate	15 26 19	9	5.36	3.89
	Medial Frontal Gyrus	-6 68 10	6	4.99	3.72
	Superior Frontal gyrus	42 44 31	9	4.94	3.70
	Rectal Gyrus	0 32 -23	13	4.50	3.48
		-9 35 -17		4.20	3.32

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.06
WM Selection Task: Cue Phase (MDD Group)

	Name	Coordinates	Cluster Extent	T	Z
*	Caudate	27 -1 34	3728	9.85	5.31
		39 -37 1		9.85	5.30
		30 -61 16		9.40	5.20
*	Precentral Gyrus	33 -31 64	989	9.48	5.22
		9 -31 70		9.10	5.13
		12 -22 70		7.43	4.66
	Insula	-39 -16 25	19	8.19	4.88
*	Cerebellum	42 -61 -32	150	8.01	4.83
		30 -61 -29		7.74	4.75
		48 -58 -20		4.97	3.71
	Cerebellum	-24 -34 -29	39	7.36	4.63
*	Cerebellum	-9 -76 -38	228	7.17	4.57
		-6 -76 -23		6.06	4.18
		9 -79 -35		5.61	4.00
	Cerebellum	33 -55 -47	40	6.55	4.36
		27 -67 -44		6.10	4.19
	Superior Frontal gyrus	-33 53 13	37	5.99	4.15
*	Middle Frontal Gyrus	39 47 31	85	5.72	4.04
		51 26 28		5.07	3.76
		39 32 25		4.41	3.43
	Cerebellum	-36 -55 -47	15	5.62	4.00
	White matter	-3 -28 -50	19	5.45	3.93
*	Inferior Parietal Lobe	39 -67 43	85	5.32	3.87
		45 -52 46		4.69	3.58
		30 -70 52		4.65	3.56

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.07
WM Selection Task: Delay Phase (MDD Group)

	Name	Coordinates	Cluster Extent	T	Z
*	IPL	45 -49 49	421	12.61	5.85
		27 -43 37		5.56	3.97
		57 -19 37		5.36	3.89
*	Posterior Cingulate	6 -55 -5	12780	10.25	5.40
		-39 -37 28		9.87	5.31
		33 -40 -29		9.82	5.30
*	Middle Frontal Lobe	-54 8 37	96	7.62	4.72
*	Post central gyrus	54 -13 19	86	7.10	4.55
		36 -28 25		4.74	3.60
		63 -13 25		3.80	3.10
*	Medial Frontal Gyrus	18 -22 55	103	6.93	4.50
		24 -16 55		6.42	4.31
		27 -4 58		5.37	3.89
*	Precuneus	15 -67 43	49	5.85	4.09
*	White matter	9 -31 -44	81	5.62	4.00
		3 -25 -44		5.54	3.97
		-3 -34 -44		5.29	3.86
	Inferior Temproral Gyrus	57 -37 25	22	5.16	3.80
	Middle Frontal Gyrus	24 53 -11	9	5.08	3.76
		24 44 -8		3.97	3.19
	Cuneus	15 -70 10	13	4.35	3.40
	Insula	45 -43 13	8	4.21	3.33
	PHG	21 -52 7	8	4.11	3.27
	Middle Frontal Gyrus	27 5 49	6	4.05	3.24

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.08
WM Selection Task: Probe Phase (MDD Group)

Name	Coordinates	Cluster Extent	T	Z
Middle Frontal Gyrus	-33 2 55	29	5.20	3.82
	-30 -1 64		4.14	3.29
Middle Frontal Gyrus	39 5 61	12	4.85	3.65
Cingulate gyrus	9 -7 46	6	4.63	3.55
Lingual Gyrus	12 -82 -5	9	4.57	3.52
Superior Temporal Gyrus	51 17 -23	9	4.47	3.47
Cuneus	27 -97 -8	14	4.42	3.44
Globus Pallidus	15 -7 -11	7	3.88	3.15

Table 3.09
Between group comparison: Stimuli phase (Controls>MDD Group)

	roi	Coordinates	Cluster Extent	T	Z
+	Left VLPFC/Insula	-39 29 4	49	4.88	4.11
		-30 17 10		4.54	3.90
		-27 26 7		3.62	3.25
	Motor Cortex	-6 5 70	9	4.77	4.05
	Left DLPFC	-39 5 28	32	4.41	3.81
	Left Premotor	-33 2 49	9	4.18	3.65
	Right SPL	33 -58 46	7	4.10	3.60
	Left DLPFC	-42 -1 43	8	4.00	3.53
	Left TOS	-27 -79 28	6	3.69	3.31

+ Significant at $p < 0.05$ following FWE correction at the cluster level.

Table 3.10
Between group comparison: Delay phase (Controls>MDD Group)

	roi	Coordinates	Cluster Extent	T	Z
+	Left VLPFC	-39 26 4	60	5.46	4.47
+	Left DLPFC	-42 -1 40	74	5.20	4.32
		-24 -4 46		4.47	3.85
	Insula	-42 14 -11	9	4.64	3.97
		-48 14 -5		3.52	3.18
	Right Thalamus/ Putamen	24 -10 19	41	4.52	3.88
		9 5 13		4.19	3.66
		15 2 19		4.00	3.53
	Left DLPFC	-51 -1 25	38	4.34	3.77
	Right DLPFC	51 14 43	13	4.25	3.70
	Right DLPFC	42 11 31	10	3.97	3.50
	Brainstem	-6 -28 -23	13	3.93	3.48
		3 -31 -29		3.74	3.34
	Right VLPFC	36 29 -11	6	3.73	3.33
	Left Ventral Striatum	-6 5 13	8	3.70	3.31
	Right Ventral Striatum	-15 5 10		3.55	3.20
	Left PCC	-6 -37 25	6	3.67	3.29

+ Significant at $p < 0.05$ following FWE correction at the cluster level.

For clusters in the vlPFC and dlPFC, $p = 0.06$ following FDR correction at the cluster level.

Table 3.11
Between group comparison: Cue phase (MDD Group>Controls)

	roi	Coordinates	Cluster Extent	T	Z
	Right Thalamus	33 -31 1	29	5.20	4.31
	Left PCC	-12 -46 16	12	5.14	4.28
	Right ACC	-15 44 7	14	4.97	4.18
	Right ACC	-15 35 10		4.04	3.56
*	Right Somatosensory	9 -40 67	94	4.63	3.96
		12 -34 55		4.42	3.81
		27 -31 58		4.30	3.73
	Subcallosal ACC	-9 32 -11	20	4.60	3.94
	Left Insula	-42 -4 -20	19	4.51	3.88
		-33 -13 -20		3.94	3.48
	Left Somatosensory	-12 -31 55	31	4.48	3.86
		-15 -40 58		4.46	3.85
		-18 -25 52		4.10	3.60
	Anterior Cingulate	3 20 7	11	4.36	3.78
	Right Ventral Striatum	27 -19 25	27	4.34	3.76
		33 -19 16		3.93	3.48
	Somatosensory	-12 -40 67	10	4.14	3.63
	Right PCC	15 -43 22	6	4.13	3.62
	Left OFA	-27 -82 -23	8	4.08	3.59
	Right STS	42 -28 28	11	4.05	3.56
	Right Somatosensory	18 -25 67	11	3.84	3.41

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.12
Conjunction Analysis: Cue Phase (All Subjects)

Name	Coordinates	Cluster Extent	T	Z
* Fusiform Gyrus	27 -67 -8	635	67.25	6.94
	21 -82 4		56.03	6.45
	33 -61 13		44.36	5.86
* Superior Parietal Lobule	-30 -61 43	477	58.09	6.55
	-39 -52 52		34.98	5.28
	-9 -64 55		27.10	4.70
* Superior Frontal Gyrus	-3 14 49	838	49.98	6.16
	-30 -1 64		45.13	5.90
	-42 29 31		35.71	5.33
* Middle Temporal Lobe	-51 -43 1	479	47.17	6.01
	-45 -64 -23		34.72	5.26
	-21 -79 4		34.63	5.26
* Anterior Cingulate	-3 35 -5	565	46.99	6.00
	9 53 16		46.23	5.96
	3 35 1		43.82	5.83
* Cerebellum	42 -67 -29	100	40.81	5.65
	36 -58 -32		25.79	4.60
* Lingual Gyrus	-27 -70 -8	103	40.36	5.62
* Superior Frontal Gyrus	-33 53 19	61	38.81	5.53
* Middle Occipiral Gyrus	30 -82 16	50	34.43	5.24
* Precuneus	-9 -49 31	194	33.56	5.19
	-12 -40 40		20.67	4.14
	-6 -67 28		18.67	3.94
* Middle Occipiral Gyrus	-27 -82 16	70	32.24	5.09

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.12
Conjunction Analysis: Cue Phase (All Subjects)
(Continued)

Name	Coordinates	Cluster Extent	T	Z
* Claustrum	-27 26 4	154	26.53	4.66
	-36 11 4		21.31	4.20
	-51 17 -2		17.48	3.81
* Inferior Parietal Lobule	39 -49 40	50	25.07	4.54
Superior Frontal Gyrus	39 44 31	72	21.07	4.18
	36 38 25		18.08	3.88
	45 29 31		17.75	3.84
Thalamus	6 -28 -5	4	20.17	4.09
* Caudate	-24 -37 10	44	19.85	4.06
	-18 -28 16		18.14	3.88
Middle Frontal Gyrus	36 2 61	33	19.56	4.03
Precuneus	9 -64 52	36	19.51	4.02
	-36 -61 -50	3	19.38	4.01
Fusiform Gyrus	-42 -34 -14	4	18.98	3.97
Caudate	-18 -10 25	26	18.77	3.95
	-24 -7 37		12.76	3.25
Postcentral Gyrus	66 -22 34	18	18.76	3.95
	63 -25 43		14.19	3.43
Cerebellum	6 -79 -32	13	16.60	3.72
Cerebellum	9 -79 -23	17	16.45	3.70

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.13
Conjunction Analysis: Delay Phase (All Subjects)

Name	Coordinates	Cluster Extent	F	Z
* Precentral Gyrus	715	-39 -13 55	40.28	5.62
		-3 8 55	39.50	5.57
		-30 -19 61	34.31	5.24
* Claustrum	76	-27 23 4	36.07	5.35
Cuneus	213	9 -85 16	29.14	4.86
		12 -73 4	22.46	4.31
		-6 -91 22	17.48	3.81
* Lentiform Nucleus	65	-15 -1 -8	27.25	4.72
		-15 8 -5	23.59	4.41
* Culmen	22	36 -46 -20	26.36	4.64
Thalamus	62	-6 -28 -5	22.43	4.30
		-6 -19 -14	17.22	3.78
		3 -28 -17	13.11	3.29
Insula	28	30 26 1	22.32	4.29
		30 23 10	14.22	3.44
Inferior Parietal Lobule	36	-66 -28 31	20.98	4.17
Parahippocampal Gyrus	36	12 5 -8	19.97	4.07
		15 -7 -11	15.53	3.59
Post Central Gyrus	9	57 -31 55	19.00	3.97
Precuneus	14	45 -70 37	18.87	3.96
Cerebellum	30	-21 -73 -26	17.43	3.81

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.13
Conjunction Analysis: Delay Phase (All Subjects)
(CONTINUED)

Name	Coordinates	Cluster Extent	F	Z
Culmen	13	9 -28 -8	17.40	3.80
		9 -25 1	13.19	3.31
Middle Frontal Gyrus	15	33 -4 49	16.72	3.73
Cerebellum	9	-39 -70 -44	15.78	3.62
Precentral Gyrus	10	12 -31 70	15.74	3.62
Superior Frontal Gyrus	6	-30 50 16	15.04	3.53
Superior Parietal Lobule	17	-27 -52 43	14.89	3.52

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.14
Conjunction Analysis: Cue Phase (Controls)

Name	Coordinates	Cluster Extent	T	Z
* Cerebellum	27 -67 -11	179	100.8	7.03
* Lingual Gyrus	-27 -73 4	55	70.60	6.29
	-33 -58 1		22.00	4.02
* Medial Frontal Gyrus	9 53 16	515	62.78	6.05
	0 32 -8		47.26	5.47
	-6 50 -8		46.40	5.44
* Cerebellum	-27 -70 -11	220	59.28	5.93
	-30 -79 -11		48.16	5.51
	-27 -82 -20		34.29	4.84
* Inferior Parietal Lobule	-33 -61 40	215	54.48	5.76
	-42 -46 43		24.91	4.24
	-39 -55 55		22.52	4.06
* Middle Occipital Gyrus	-27 -82 16	89	48.80	5.54
	-24 -88 22		41.99	5.24
	-42 -73 4		22.96	4.10
* Middle Occipital Gyrus	27 -88 19	72	46.27	5.43
* Precuneus	-9 -46 31	154	41.61	5.22
	-12 -40 37		27.54	4.43
	-9 -49 19		21.38	3.97
* Middle Frontal Gyrus	-33 -4 64	109	33.03	4.77
	-24 -7 52		22.48	4.06
	-12 8 70		19.54	3.82
* Superior Frontal Gyrus	-33 50 19	31	32.66	4.75
* Middle Frontal Gyrus	-45 35 34	90	26.80	4.38

Table 3.14
Conjunction Analysis: Cue Phase (Controls)
(CONTINUED)

Name	Coordinates	Cluster Extent	T	Z
* Middle Temporal Gyrus	-54 -43 4	54	26.38	4.35
	-60 -28 -2		15.57	3.43
	-63 -37 4		14.93	3.37
Lingual Gyrus	21 -82 4	33	26.32	4.34
	30 -70 4		22.89	4.09
	33 -58 13		22.56	4.07
Superior Parietal Lobule	-9 -67 52	13	23.75	4.16
Superior Frontal Gyrus	-3 14 49	37	22.37	4.05
Insula	-36 11 7	10	20.95	3.94
Parahippocampal Gyrus	36 -46 1	24	20.82	3.92
Cerebellum	45 -67 -26	19	19.85	3.84

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.15
Conjunction Analysis: Delay (Control Group)

Name	Coordinates	Cluster Extent	T	Z
* Claustrum	-27 23 4	82	36.29	4.95
	-39 11 7		15.61	3.44
* Thalamus	-6 -28 -2	54	35.43	4.91
	-6 -19 -11		20.67	3.91
* Superior Frontal Gyrus	-3 8 55	78	32.47	4.74
	-6 -1 64		14.10	3.28
Precentral Gyrus	-42 -1 40	272	32.17	4.72
	-39 -22 52		30.32	4.61
	-42 -7 49		29.75	4.57
Culman	36 -43 -20	9	29.71	4.57
Middle Frontal Gyrus	33 -4 46	51	27.88	4.45
	42 -1 46		19.95	3.85
Cuneus	-9 -94 22	20	27.09	4.40
Thalamus	9 -28 1	23	24.60	4.22
	6 -19 1		14.16	3.28
Inferior Frontal Gyrus	33 26 4	26	23.87	4.17
Cuneus	9 -88 13	63	22.41	4.05
	15 -73 -2		22.40	4.05
	12 -79 7		14.72	3.34
Lentiform Nucleus	-18 11 -2	49	20.94	3.94
	-15 5 -11		15.59	3.44
Inferior Parietal Lobule	-66 -28 31	13	20.65	3.91
Superior Parietal Lobule	-27 -52 43	28	20.46	3.89
Cingulate Gyrus	-9 17 34	9	18.11	3.68

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.16
Selection>NonSelection: Cue Phase (Healthy Controls)

	roi	Coordinates	Cluster Extent	T	Z
*	Left IPL	-36 -37 31	79	12.12	5.76
		-39 -37 49		11.22	5.59
		-42 -34 37		5.50	3.95
*	Cerebullum	24 -52 -23	62	9.90	5.32
*	Right ACC	18 29 13	103	7.16	4.57
		24 17 31		6.90	4.48
		21 11 13		4.96	3.71
*	Right Precentral Gyrus	36 -1 -32	13	6.60	4.38
*	Left Caudate	-24 14 22	47	6.38	4.30
		-18 14 37		4.85	3.65
		-21 2 25		4.68	3.57
*	Left Anterior Cingulate	-6 -4 34	50	6.29	4.27
		-6 8 28		6.08	4.19
	Left Insula	-30 -19 22	20	6.05	4.17
*	Left Precentral Gyrus	-27 -7 52	37	5.91	4.12
		-18 5 58		5.13	3.79
		-18 -4 64		4.34	3.40
*	Right Caudate	15 17 -5	33	5.90	4.11
		21 26 -5		4.58	3.52
		18 8 -8		4.21	3.33
	Right MFG	45 -43 25	6	5.25	3.84
		54 -46 22		4.06	3.25
	Left Caudate	-15 20 -2	8	5.19	3.81
	Cerebullum	-18 -64 49	6	5.17	3.81
	Right Caudate	36 -25 -5	10	5.09	3.77
		45 -22 -2		5.03	3.74
	Right Middle Frontal Gyrus	42 2 40	10	5.04	3.75
	Left Precentral Gyrus	-33 29 34	6	4.94	3.70
	White Matter	-27 38 -5	12	4.87	3.66

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.17
Selection>NonSelection: Cue Phase (MDD Group)

	roi	Coordinates	Cluster Extent	T	Z
*	Cuneus	12 -70 19	196	6.23	4.24
		15 -73 7		5.84	4.09
		6 -61 1		5.50	3.95
*	Superior Temportal Gyrus	57 2 -8	9	6.00	4.15
		54 -4 -2		4.41	3.44
		-24 -16 -11	7	5.95	4.14
	Anterior Cingulate	-6 38 13	8	5.74	4.05
	Caudate	-6 11 -8	15	5.52	3.96
		-3 2 -2		4.77	3.62
		3 -25 -41	9	5.46	3.93
	Amygdala	33 8 -11	12	5.24	3.84
		36 14 -5		5.04	3.75
		15 11 -5	8	4.73	3.60
	Cuneus	27 -73 37	6	4.72	3.59
	Anterior Cingulate	9 38 13	6	4.63	3.55
	Inferior Occipital Gyrus	-12 -91 1	6	4.63	3.54
	Inferior Occipital Gyrus	-42 -82 7	12	4.31	3.38
		-36 -82 16		4.08	3.26

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.18
Face>NonSelection: Cue Phase (Healthy Controls)

	Name	Coordinates	Cluster Extent	T	Z
	Left IPL	-39 -37 46	20	7.93	4.81
*	Precentral Gyrus	-27 -7 49	79	7.83	4.78
		-21 -4 58		5.23	3.83
		-21 5 61		4.73	3.60
*	Cerebellum/PHG	27 -49 -26	37	6.87	4.47
		21 -52 -20		6.13	4.20
	Left Insula	-30 -19 22	15	6.30	4.27
	White Matter	24 29 7	16	5.29	3.86
		24 32 -2		5.05	3.75
	Left Premotor	-9 -4 43	18	4.91	3.68
		-3 2 52		4.55	3.51
		6 -1 52		4.09	3.27
	Left Middle Frontal Gyrus	-33 32 31	15	4.69	3.58
	Left Insula	-42 -40 28	6	4.65	3.56
	Right Middle Temporal Sulcus	51 2 1	9	4.61	3.54
	Left Middle Cingulate	-12 11 40	6	4.55	3.51
	Left Middle Cingulate	12 5 40	10	4.47	3.47

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.19
NonSelection>Face: Cue Phase (Healthy Controls)

	Name	Coordinates	Cluster Extent	T	Z
	pgACC	0 35 -11	14	6.40	4.31
	Right Thalamus	24 -13 -17	9	6.31	4.27
*	Precuneus	6 -64 37	44	6.25	4.25
		-6 -61 40		4.89	3.68
		12 -52 40		4.18	3.31
*	Left RSC	-9 -52 10	51	6.15	4.21
		-21 -58 16		4.11	3.27
	Left PHG	-30 -22 -17	6	5.84	4.09
	Left TOS	-33 -79 37	19	5.26	3.84
		-39 -70 46		4.80	3.63
		-45 -64 40		3.93	3.17
*	Left PHG	-30 -40 -11	31	5.21	3.82
	Precuneus	-3 -67 25	6	4.75	3.61
	left PHG	-24 -49 1	6	4.72	3.59
	Right RSC	12 -52 10	19	4.70	3.58
		9 -43 7		4.63	3.55

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.20
Scene>NonSelection: Cue Phase (Healthy Controls)

	Name	Coordinates	Cluster Extent	T	Z
*	Right Anterior Cingulate	18 29 13	121	7.54	4.69
		21 29 34		6.69	4.41
		27 14 34		6.24	4.25
*	DLPFC	-42 38 7	28	7.39	4.64
*	Left Caudate	-15 23 -2	45	7.11	4.55
		-9 14 -5		5.95	4.13
*	Cerebllum	30 -46 -26	85	6.91	4.49
		30 -40 -17		6.37	4.29
		24 -52 -23		5.95	4.14
*	Precuneus	-15 -67 49	52	6.84	4.46
		-24 -61 55		5.29	3.86
*	Left IPL	-42 -37 49	64	6.75	4.43
		-42 -34 37		5.92	4.12
		-30 -37 31		4.40	3.43
*	White matter	-27 44 -2	43	6.64	4.39
	Cerebellum	-6 -67 -29	6	6.38	4.30
*	Left Anterior Cingulate	-21 17 25	45	6.32	4.28
		-27 2 22		5.97	4.14
		-24 5 13		4.79	3.62
*	Middle Cingulate	-9 -10 34	69	6.07	4.18
		3 -1 28		5.50	3.95
		-6 5 31		4.96	3.71

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.20
Scene>NonSelection: Cue Phase (Healthy Controls)
(CONTINUED)

	Name	Coordinates	Cluster Extent	T	Z
*	Left Middle Temporal	-54 -43 -8	27	5.95	4.13
		-51 -55 -11		5.46	3.93
*	Left Middle Temporal	-30 -67 28	51	5.74	4.05
		-30 -82 28		5.42	3.91
	Right Lingual Gyrus	21 -91 7	17	5.70	4.04
	Right TOS	39 -73 34	51	5.43	3.92
		36 -64 34		4.58	3.52
		45 -70 28		4.37	3.41
*	Left Cingulate Gyrus	-3 26 37	25	5.38	3.90
	Left PHG	-36 -64 -8	7	5.33	3.88
*	Putamen	24 11 10	27	5.29	3.86
		15 14 16		4.45	3.46
		15 5 7		4.14	3.29
*	Right Caudate	15 17 -5	24	5.25	3.84
	Right Caudate	24 -1 22	8	5.24	3.84
		-33 14 58	12	5.21	3.82
		-27 8 61		3.98	3.20
	Left Precentral Gyrus	-36 17 37	10	5.00	3.72
	Right DLPFC	42 8 40	19	4.82	3.64
	Left Putamen	-30 -10 -2	9	4.81	3.64
	Right Insula	39 5 -29	8	4.76	3.61
	Right Claustrum	30 20 -5	10	4.69	3.58
	Left PHG	-42 -37 -8	8	4.56	3.51
	Right PHG	42 26 10	15	4.49	3.48
	Left Cingulate Gyrus	-18 14 37	7	4.35	3.40
	Left Precentral Gyrus	-45 26 34	14	4.23	3.34
		-33 29 34		4.21	3.33

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.21
Scene>NonSelection: Cue Phase (MDD Group)

	Name	Coordinates	Cluster Extent	T	Z
*	Cuneus	15 -70 22	284	7.10	4.55
		-9 -73 16		6.52	4.35
		-21 -76 31		6.20	4.23
*	Cerebellum	-33 -52 -17	88	6.71	4.42
		-36 -34 -17		5.57	3.98
		-21 -46 -8		4.16	3.30
*	Right vSTS	51 -4 -5	65	6.08	4.19
		60 2 -11		5.83	4.09
		54 -13 7		4.35	3.40
	Left Thalamus	-18 -19 -5	17	6.00	4.15
		-27 -25 -14		5.11	3.78
	Right Claustrum	33 -1 -8	15	5.93	4.13
		33 8 -11		4.63	3.55
*	Precuneus	30 -70 34	40	5.66	4.02
		36 -79 40		4.41	3.44

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.21
Scene>NonSelection: Cue Phase (MDD Group)
(Continued)

Name	Coordinates	Cluster Extent	T	Z
Left MFG	-51 29 28	12	5.38	3.90
Left Caudate	-6 11 -8	8	5.26	3.84
Right Precentral Gyrus	54 8 43	13	5.09	3.77
	57 14 37		4.53	3.50
Left DMPFC	-18 35 34	6	5.02	3.74
Left IOG	-12 -94 -2	15	4.98	3.72
DMPFC	-9 44 49	8	4.93	3.69
Left vSTS	-54 -4 -8	10	4.84	3.65
Right TOS	39 -76 25	18	4.82	3.64
	42 -73 10		4.09	3.27
Left Cingulate	-6 44 10	9	4.82	3.64
Left Insula	-36 -28 7	9	4.56	3.51
Left IOG	-42 -85 7	6	4.43	3.44
Right PHG	39 -31 -17	10	4.41	3.43
Right Thalamus	21 -25 -8	7	4.06	3.24
	15 -19 -11		3.91	3.16

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.22
Scene>NonSelection: Probe Phase (Healthy Controls)

	Name	Coordinates	Cluster Extent	T	Z
*	Left TOS	-33 -82 31	209	10.26	5.40
		-42 -79 22		6.96	4.50
		-30 -82 13		5.82	4.08
*	Left PHG	-30 -49 -8	145	10.16	5.38
		-27 -43 -17		9.09	5.12
		-27 -58 -14		5.18	3.81
*	Right PHG	30 -46 -8	190	10.03	5.35
		24 -52 -11		9.47	5.22
		24 -31 -17		8.10	4.86
*	Right TOS	33 -76 16	299	7.86	4.79
		42 -79 19		7.47	4.67
		33 -85 19		7.21	4.59
*	Right RSC	12 -52 10	45	6.71	4.42
		18 -52 19		6.10	4.19
		3 -55 10		4.82	3.64
*	Left RSC	-12 -52 13	24	5.39	3.90

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.23
Scene>NonSelection: Probe Phase (MDD Group)

	Name	Coordinates	Cluster Extent	T	Z
*	Left Caudate	-36 -79 4	92	7.38	4.64
		-30 -82 19		4.52	3.49
		-21 -85 4		4.31	3.38
*	Right TOS	36 -76 31	190	6.95	4.50
		30 -70 13		5.02	3.74
		42 -85 10		4.59	3.53
*	APFC	3 59 34	145	6.74	4.43
		15 44 43		5.96	4.14
		6 44 40		5.83	4.09
	Right PHG	36 -43 -8	126	6.51	4.35
		27 -43 -14		5.75	4.05
		30 -31 -17		5.55	3.97

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.24
Clusters that positively correlate with Response Accuracy (Control Group)

Name	Coordinates	Cluster Extent	T	Z
Supramarginal gyrus	-36 -37 31	69	13.56	5.86
	-39 -37 49		10.83	5.39
	-42 -34 37		5.32	3.81
Cerebellum	24 -52 -23	65	9.78	5.17
Anterior Cingulate	18 29 13	107	7.26	4.51
	24 17 31		6.65	4.32
	21 11 16		5.09	3.71
Caudate	36 -1 -32	12	6.70	4.33
Cingulate	-21 17 28	96	6.19	4.16
	-6 -4 34		6.13	4.13
	-6 8 28		5.88	4.04

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.24
Clusters that positively correlate with Response Accuracy (Control Group) (Continued)

Name	Coordinates	Cluster Extent	T	Z
Superior Temporal Gyrus	48 -43 25	7	6.16	4.14
Insula	-30 -19 22	19	6.08	4.11
Left PHG	-42 -34 -8	8	5.92	4.05
Caudate	15 17 -5	22	5.71	3.97
	21 26 -5		4.82	3.59
	18 8 -8		4.11	3.23
Middle Frontal Gyrus	-27 -7 52	16	5.70	3.96
Caudate	-15 20 -2	6	5.37	3.83
Middle Frontal Gyrus	-18 5 61	14	5.31	3.81
Claustrum	42 -22 -2	7	5.28	3.79
Middle Frontal Gyrus	39 2 37	12	4.90	3.63
Precentral Gyrus	-57 8 31	7	4.84	3.60

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.25
Clusters that positively correlate with OSPAN (Control Group)

	Name	Coordinates	Cluster Extent	T	Z
	Supramarginal gyrus	-39 -37 49	74	12.01	5.61
		-36 -37 31		11.71	5.55
		-42 -34 37		5.32	3.81
	Cerebellum	24 -52 -23	56	9.85	5.19
	ACC	24 17 31	94	8.50	4.86
		18 29 13		6.95	4.42
		18 23 31		6.38	4.22
*	Cingulate	-27 -22 22	18	7.50	4.59
	Uncas	36 -1 -32	11	7.32	4.53
	Precuneus	-18 -64 49	7	6.38	4.22
	Cingulate Gyrus	-6 -4 34	43	6.28	4.19
		-6 8 28		6.01	4.09
	Left MFG	-24 14 22	40	6.28	4.18
		-18 14 37		5.74	3.98
		-21 2 28		4.60	3.48

* * Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.25
Clusters that positively correlate with OSPAN (Control Group) (Continued)

Name	Coordinates	Cluster Extent	T	Z
Caudate	15 17 -5	23	5.87	4.04
	18 8 -8		4.39	3.38
Precentral Gyrus	-33 29 34	6	5.81	4.01
Left MFG	-27 -7 52	21	5.76	3.99
	-18 -4 64		4.24	3.30
Precentral Gyrus	39 2 40	10	5.43	3.86
	-18 5 58	11	5.31	3.81
Lingual Gyrus	18 -91 10	6	5.28	3.79
Caudate	-15 20 -2	6	5.00	3.67
Caudate	21 11 13	10	4.81	3.58
Left MFG	-27 38 -5	9	4.78	3.57
Precentral Gyrus	-57 5 28	6	4.76	3.56

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.26
Clusters that positively correlate with Response Accuracy (MDD Group)

Name	Coordinates	Cluster Extent	T	Z
Cuneus	12 -70 19	269	6.98	4.43
	-6 -70 13		6.49	4.26
	18 -70 7		6.17	4.15
Globus Pallidus	-24 -16 -11	9	6.74	4.35
Superior Temporal Gyrus	57 2 -8	6	5.79	4.00
	54 -4 -2		4.28	3.32
Anterior Cingulate	-6 38 13	6	5.75	3.99
	3 -25 -41	8	5.68	3.96
Caudate	-6 11 -8	13	5.58	3.92
	-3 2 -2		4.76	3.56
Claustrum	33 8 -11	11	5.10	3.71
	36 14 -5		4.93	3.64
PHG	-18 -52 4	6	4.45	3.41
Left MOG	-39 -85 10	9	4.33	3.35

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.27
Clusters that positively correlate with OSPAN (MDD Group)

Name	Coordinates	Cluster Extent	T	Z
Cuneus	15 -73 7	151	8.54	4.88
	12 -70 19		6.73	4.34
	6 -61 1		5.83	4.02
Cuneus	-12 -76 7	58	5.90	4.05
	-15 -70 1		4.91	3.63
	-18 -85 25		4.81	3.58
ACC	-6 11 -8	14	5.81	4.01
	-3 2 -2		4.80	3.58
Superior Temporal Gyrus	57 2 -8	6	5.78	4.00
	54 -4 -2		4.29	3.33
	3 -25 -41	6	5.30	3.80
Claustrum	33 8 -11	10	5.23	3.77
			4.87	3.61
Left MOG	-42 -82 7	6	4.16	3.26

* Significant at $p < 0.05$ following FDR correction at cluster level.

Table 3.28
ROI Coordinates

ROI	x	y	z
ACC (Right)	9	27	30
BG	15	0	10
Cerebellum	42	-45	-30
Cuneus	10	-85	24
Cuneus	12	-90	30
IFG (Right)	33	21	-3
IFL (Left)	-33	21	0
IPL (Left)	-45	-39	42
IPL (Right)	45	-39	45
IPS (Left)	-21	-60	63
IPS (Right)	30	-63	48
MFG (Left)	-33	48	12
MFG (Left)	-42	30	24
MFG (Load)	-36	21	42
MFG (Right)	36	57	-6
MFG (Right)	48	30	24
MOG (Left)	-45	-75	-3
MOG (Right)	45	-78	0
Motor	-35	-16	55
MT (Left)	-54	-54	-6
PM (Right)	21	3	69
Precuneus (Left)	-42	0	30
Precuneus (Right)	15	-63	63
SFS (Left)	-24	-3	57
SFS (Right)	24	0	51
SMA	0	15	48
SPL (Left)	-21	-66	60
Thalamus (Right)	16	-20	14