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Flexibly adapting to emotional cues: Examining the functional and structural correlates of emotional reactivity and emotion control in healthy and depressed individuals

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A thesis submitted in partial fulfillment of the requirements for the degree in Doctor of Philosophy
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FLEXIBLY ADAPTING TO EMOTIONAL CUES: EXAMINING THE FUNCTIONAL
AND STRUCTURAL CORRELATES OF EMOTIONAL REACTIVITY AND EMOTION
CONTROL IN HEALTHY AND DEPRESSED INDIVIDUALS

(Thesis format: Integrated Article)

by

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Graduate Program in Anatomy and Cell Biology

A thesis submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy

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Abstract

The ability of emotionally significant stimuli to bias our behaviour is an evolutionarily adaptive phenomenon. However, sometimes emotions become excessive, inappropriate, and even pathological, like in major depressive disorder (MDD). Emotional flexibility includes both the neural processes involved in reacting to, or representing, emotional significance, and those involved in controlling emotional reactivity. MDD represents a potentially distinct form of emotion (in)flexibility, and therefore offers a unique perspective for understanding both the integration of conflicting emotional cues and the neural regions involved in actively controlling emotional systems.

The present investigation of emotional flexibility began by considering the functional neural correlates of competing socio-emotional cues and effortful emotion regulation in MDD using both negative and positive emotions. Study 1 revealed greater amygdala activity in MDD relative to control participants when negative cues were centrally presented and task-relevant. No significant between-group differences were observed in the amygdala for peripheral task-irrelevant negative distracters. However, controls demonstrated greater recruitment of the ventrolateral (vlPFC) and dorsomedial prefrontal cortices (dmPFC) implicated in emotion control. Conversely, attenuated amygdala activity for task-relevant and irrelevant positive cues was observed in depressed participants. In Study 2, effortful emotion regulation using strategies adapted from cognitive behaviour therapy (CBT) revealed greater activity in regions of the dorsal and lateral prefrontal cortices in both MDD and control participants when attempting to either down-regulate negative or up-regulate positive emotions. During the down-regulation of negative cues, only controls displayed a significant reduction of amygdala activity. In Study 3, an individual differences approach using multiple regression revealed that while greater amygdala-vmPFC structural connectivity was associated with low trait-anxiety, greater connectivity between amygdala and regions of occipitotemporal and parietal cortices was associated with high trait-anxiety.

These findings are discussed with respect to current models of emotional reactivity and emotion control derived from studies of both healthy individuals and those with emotional disorders, particularly depression. The focus is on amygdala variability in differing

contexts, the role of the vmPFC in the modulation of amygdala activity via learning processes, and the modulation of emotion by attention or cognitive control mechanisms initiated by regions of frontoparietal cortices.

Keywords

Emotion; regulation; emotion regulation; emotion control; amygdala; prefrontal cortex; functional neuroimaging; functional magnetic resonance imaging; diffusion-weighted imaging; cognitive neuroscience; structural connectivity; tractography

Co-Authorship Statement

Chapter 1, the introduction, and Chapter 5, the general discussion and future directions, were written by Steven Greening with input from Derek Mitchell. Chapter 2 entitled “Emotion-related brain activity to conflicting socio-emotional cues in unmedicated depression” was written by Steven Greening with input from all co-authors. Derek Mitchell, Elizabeth Osuch and Peter Williamson were involved in the conception of the experiment. Derek Mitchell and Steven Greening designed the experiment and collected the data. Chapter 3 entitled “The neural correlates of regulating positive and negative emotions in medication-free major depression” was written by Steven Greening with input from all co-authors. Derek Mitchell, Elizabeth Osuch and Peter Williamson were involved in the conception of the experiment. Derek Mitchell and Steven Greening designed the experiment and collected the data. Chapter 4 entitled “A network of amygdala connections predict individual differences in trait-anxiety” was written by Steven Greening with input from Derek Mitchell.

To the memory of Yet-Wo Loo and Yet-Ping Loo

Acknowledgments

*Two roads diverged in a wood, and I,
I took the one less traveled by,
And that has made all the difference*
— Robert Frost

Five years ago I embarked on the journey of “graduate school”. At the time I was a bright youth with a thirst for knowledge who hoped to learn everything there was to know about the brain. Five years later, I am, in my own estimation, older and duller, though I believe my thirst for knowledge remains insatiable. I have indeed learned a great deal that I had not known before. But what I have learned foremost is how little we really know about the brain, how vast the expanse of our ignorance really is, and how my own ignorance is greater still. Although I was aware of Einstein’s certainty of the infinite expanse of human stupidity, as a simple minded human, I had to learn this lesson the hard way. Graduate school has been my hard way; my rite of passage; my “road less traveled by”. Nevertheless, there are some things which I have learned for certain. For one, I know that graduate school is not something that one undertakes and completes alone. Thus, I would like to make the following acknowledgements.

To Derek Mitchell, thank you for taking a long-shot for your first doctoral student and betting on the dark horse. With your help and expertise, the past five years have been quite a productive ride; and it is amazing how fast five years flew by. To the members of the Mitchell lab, past and present, I consider you all comrades-in-arms, collaborators, and friends, and I thank you all. To James Kryklywy in particular, thank you for spreading your virulent need for automaticity. The creation of regressors will never be the same. I would also like to thank FEMAP, and the emotion regulation program that was once at South Street Hospital, without which this research may have never been completed. Thanks to CFMM and its members for the help with scanning. Thanks to the tax payers of Canada and Ontario, whose contributions meant my studies could be supported by NSERC and OGS scholarships.

To all my friends who offered me support and condolences along the way, thank you. Although after five years we still really do not understand each other’s research, Chris Elliott and I shared the inexplicable experience of graduate school. I would like to thank Chris for

his friendship and insistence on coffee breaks, without both of which I may not have made it out alive (or I would have been a little more tired).

To my family, thank you for trusting me in my stubborn pursuit of seemingly unending higher-education. Despite your – and at times my own – better judgment, my insinuations on unemployment may yet come to an end. To my mother, you taught me through both words and actions the value of hard-work; that a commitment is something real, tangible, and unbreakable; that the words ‘quit’ and ‘cannot’, are words not to be used readily. Foremost, you taught me that the greatest things in life are not material possessions, but instead they are the feelings we get when we have changed the world, even if ever so slightly, for the better. To my sister, Diane, thank you for your unconditional love and support; Gavin is lucky to have such a great mother. Dad and Ken, thank you both for taking me in out of the cold when, in undergrad, I was too hard-up to pay for summer rent (because at the time I was already beginning to pursue research, which meant I couldn't afford rent); and for your unquestioning support as I pursued questions of the brain and mind.

And finally, to my wife, it has been said “alongside any good man is a great woman”. Emily, you have proven not only the validity, but the necessity of this too true idiom. You have been there to pick me up when I was down, and you have been there to hold me up when I was up. You are my muse, and you are my champion. You have been there throughout this process, and you are the perfect reminder that beyond the litany of data and abstractness within which I toil, there is a beautiful and holistic life to be led. Thank you for your support, for your understanding, and for your endless encouragement.

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List of Abbreviations

BA	Broadmann's area
BOLD	blood-oxygenation dependent signal
CBT	cognitive behavioural therapy
dIPFC	dorsolateral prefrontal cortex
dmPFC	dorsomedial prefrontal cortex
DTI	diffusion-weighted imaging
fMRI	functional magnetic resonance imaging
IFG	inferior frontal gyrus
IPL	inferior parietal lobe
MDD	major depressive disorder
mOFC	medial orbitofrontal cortex
mPFC	medial prefrontal cortex
NAcc	nucleus accumbens
OFC	orbitofrontal cortex
PET	positronic emission tomography
PFC	prefrontal cortex
pgPFC	perigenual prefrontal cortex
rACC	rostral anterior cingulate cortex
sgPFC	subgenual prefrontal cortex
SSRI	selective-serotonin reuptake inhibitor
TPJ	temporoparietal junction
vIPFC	ventrolateral prefrontal cortex
vmPFC	ventromedial prefrontal cortex

CHAPTER 1

1 INTRODUCTION

1.1 Setting the scene for emotional flexibility

Walking through the woods, you spot a snake on the path. You experience a rapid increase in heart rate and sweating, and perhaps let out a shout of fright. In this scenario the appropriate response is to flee hastily, or fight valiantly. Yet, if you realized that the snake was actually a stick, your heart rate and sweat production would decrease. This decrease could come about reflexively or automatically, maybe even before you have time to shout; or through conscious effort, by slowing your breathing and telling yourself: "it's a stick, not a snake," or by focusing your gaze away from the stick and towards a nearby butterfly. Or, all of these processes might occur simultaneously to various degrees, thus facilitating the appropriate response to continue on your leisurely walk.

This example serves to underline the main focus of this introduction and subsequent chapters, emotional flexibility and two related sub-components. The first part of the scenario highlights emotional reactivity, while the latter part emphasizes emotion control. In humans, flexibly responding to emotional cues appears to involve the integration of at least these two processes. Indeed, this ability to flexibly adapt to emotional cues appears to be an evolutionarily advantageous characteristic necessary for survival (LeDoux, 2012). However, some combination of these processes can go awry and give rise to a number of psychiatric conditions. Major depressive disorder (MDD), in particular, represents a prevalent, disabling, and costly example of emotion dysfunction (World Health Organization, 2003). And, it is estimated that the lifetime prevalence of mood disorders, including bipolar and unipolar depression, is greater than 20% (Kessler, Berglund, et al., 2005).

Within the brain, discussions of emotional reactivity often emphasize the role and importance of the amygdala (Zald, 2003). On the other hand, at least three distinct regions of the prefrontal cortex are consistently implicated in emotion control (Mitchell, 2011; Ochsner & Gross, 2005): aspects of the ventromedial prefrontal cortex (vmPFC), the ventrolateral prefrontal cortex (vlPFC) including parts of the inferior frontal gyrus (IFG), and dorsal regions of prefrontal cortex, including dorsolateral prefrontal cortex

(dlPFC) and dorsomedial prefrontal cortex (dmPFC). Indeed, abnormalities in the amygdala and the regions associated with emotion control have been observed within psychiatric disorders that feature abnormal emotional responding, for example depression (Drevets et al., 1992; Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007; Light et al., 2011). Nevertheless, to date the neurocognitive mechanisms of emotion reactivity and control, including aspects of both function and structure, remain underspecified in the literature.

So as to adequately reflect the three research chapters, the remainder of the introduction covers the topic of emotional reactivity and emotion control from multiple perspectives, while also indicating some of the existing debates and unknowns in the literature. The multiple perspectives taken in the research chapters includes studies of depressed and healthy control participants, and multiple neuroimaging modalities (i.e., functional magnetic resonance imaging, fMRI, of the blood oxygen level dependent, BOLD, signal; and diffusion-weighted imaging, DWI, as a measure of structural connectivity).

1.2 Emotions and their neural representation

1.2.1 An operational definition of emotion

Emotions can be described as states elicited by either rewarding or punishing stimuli (i.e., reinforcers), which serve to motivate behaviour (Rolls, 2000); a rewarding stimulus is anything an organism will work to obtain or approach, and a punisher is anything an organism will work to avoid. Many models of emotion emphasize that emotions arise from, and mediate, the relationship between reinforcers and behavioural responses, or stimulus-response contingencies (Adolphs, 2013; Gross & Thompson, 2007; LeDoux, 2012; Salzman & Fusi, 2010). Consistent with dimensional theories of emotion (Lang, Bradley, & Cuthbert, 1998; Russell, 1980), the degree of emotional reactivity can, therefore, be understood as the valence (i.e., positive versus negative, or

rewarding versus punishing) and intensity (or arousal) associated with the elicited state. Finally, emotions are rapid and transient states, which may contribute to moods which are longer lasting (Gross & Thompson, 2007; Rolls, 2000).

Quantifying and inferring emotional reactivity can be done in a number of ways, including: Measuring peripheral physiological responses, such as sweating, heart rate, or pupil diameter (Bradley, Miccoli, Escrig, & Lang, 2008); having participants self-report on a rating scale (Lang, Greenwald, Bradley, & Hamm, 1993); or by measuring activity in brain regions which appear to encode and represent emotional reactivity, such as the amygdala (Phelps et al., 2001).

1.2.2 Neural representation of emotion

In terms of the brain, the current definition of emotion also fits well with suggestions that emotions arise from the activation of survival circuits (LeDoux, 2012) or neural networks (Salzman & Fusi, 2010) that represent the various processes involved in translating a reinforcer to behaviour. These circuits or networks include brain regions implicated in perception, memory, attention, and motor responding, in addition to those regions encoding the emotional significance (i.e., valence and intensity) of the reinforcers. While the latter process of encoding emotional significance will be discussed below, aspects of the former processes will be relevant to discussions of emotion control in a later section.

We can begin to infer emotional reactivity by measuring fluctuations in brain activity that vary as a function of the emotional content of a given stimulus, or in other words we can measure changes to the potential representation of emotions. Here emotion representation refers to activity in the brain that is augmented by the emotional significance of either external (e.g., objects in the environment) or internal cues (e.g., memories of emotional objects), and will be used interchangeably with discussions of emotional reactivity. This does not necessarily mean that regions identified in this manner are needed for emotional reactivity or for the generation of emotions per se, but

rather that they reflect some measurable aspect of emotional significance. These regions tend to appear stimulus-driven (or bottom-up) and are activated in response to rewarding or punishing stimuli. For example, if we observe greater activity in brain region 'X' in response to viewing a picture of an unknown actor making a fearful facial expression relative to the amount of activity in 'X' after viewing the same actor making a neutral expression, we would say region 'X' is representing the emotional significance of the face stimulus. This inference is at least partially supported because we have controlled for certain confounding process, like visual complexity (the same actor), or memory (that actor was unfamiliar), eye movements (assuming that participant maintained their eye gaze), or attention (the participant maintained focused on the task). Like region 'X', the amygdala, a collection of nuclei in the anteromedial temporal lobe, appears to be one of the critical brain regions involved in the representation of emotions (Phelps, 2006). Other regions such as extrastriate visual cortex in occipitotemporal regions also appear modulated as a function of emotional significance (e.g., Pessoa et al., 2002).

Perhaps the richest body of literature regarding the amygdala's importance in the acquisition of emotional significance comes from studies involving Pavlovian fear conditioning. In fear conditioning an initially neutral stimulus acquires emotional significance through repeated pairing with an aversive stimulus such as a mild shock. Impairments in fear conditioning have been observed following lesions or damage to the amygdala across a number of species, including rats (Nader, Majidishad, Amorapanth, & LeDoux, 2001; Phillips & LeDoux, 1992), monkeys (Antoniadis, Winslow, Davis, & Amaral, 2007, 2009), and humans (Bechara et al., 1995; LaBar, LeDoux, Spencer, & Phelps, 1995). Functional brain imaging, including functional magnetic resonance imaging (fMRI), in humans has further demonstrated that fear-related amygdala activity positively correlates with individual differences in autonomic reactivity (Phelps et al., 2001) and personality measures of anxiety (Bishop, Jenkins, & Lawrence, 2007). In addition to fear or aversive associations, the amygdala also encodes appetitive or positive associations (Amting, Miller, Chow, & Mitchell, 2009; Belova, Paton, & Salzman, 2008; Paton, Belova, Morrison, & Salzman, 2006), and may also be positively correlated with individual differences in reward-related processes (Beaver et al., 2006; Hamann, Ely, Grafton, & Kilts, 1999). However, it should be noted that relatively less is known about

the role of the amygdala in appetitive compared to aversive processes. Nevertheless, relevant to discussions of emotional flexibility, the amygdala displays the ability to respond and adapt to changes to the emotional significance of both positive and negative stimuli.

The amygdala also appears particularly sensitive to the encoding of socio-emotional cues, including fearful expressions in particular (Adolphs, Tranel, Damasio, & Damasio, 1994; Anderson & Phelps, 2000), but also disgust, sadness, and happiness (Anderson & Phelps, 2000). Evidence from both lesion (Adolphs, Tranel, Damasio, & Damasio, 1995) and functional (Gamer & Buchel, 2009; Han, Alders, Greening, Neufeld, & Mitchell, 2012) studies of the amygdala appear to indicate that one role of the amygdala is to signal the presence of an emotionally significant cue in the environment (e.g., the eyes in the identification of fearful facial expressions) and bias attention to that location. Moreover, the amygdala contributes to observations that emotional cues receive prioritized processing. Lesions to the amygdala impaired the attention enhancing effects of emotional cues (Anderson & Phelps, 2001). Additionally, while lesions to the amygdala abolish emotion-evoked increases in visual brain activity (Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004), patients with both cortical blindness (de Gelder, Vroomen, Pourtois, & Weiskrantz, 1999) and visual neglect (Vuilleumier & Schwartz, 2001) still display facilitated responses to emotional cues despite perceptual impairment. Lastly, functional activation of the amygdala by distracting emotional cues is associated with impaired cognitive performance (Dolcos & McCarthy, 2006; Mitchell et al., 2008). Thus, the data suggests that the amygdala is an important region for the encoding of emotional significance and may be a hub at the centre of a network of regions implicated in emotion related behaviour. Finally, although research in humans suggests that emotions can be experienced (Anderson & Phelps, 2002; Feinstein et al., 2013) and generated (Anderson & Phelps, 2000) in the absence of intact amygdalae, electrical stimulation of the human amygdala is sufficient to produce the subjective experience of both positive and negative emotions (Lanteaume et al., 2007).

A number of other regions appear to play a role in the representation of various emotions or emotional properties. The nucleus accumbens (NAcc) is implicated in the

representation of punishment and reward history and appears to bias behaviour accordingly (Carlezon & Thomas, 2009). The anterior insula appears to be preferentially activated by negative stimuli (Anderson et al., 2003; Small et al., 2003), to encode states of autonomic arousal (Cechetto & Shoemaker, 2009), and appears to reflect the appraisal of internal bodily states (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004). Aspects of the orbitofrontal cortex (OFC) appear to preferentially encode reward (Anderson et al., 2003), though it is also sensitive to changes in punishment (Morrison & Salzman, 2009) and may modulate amygdala activity (Morrison, Saez, Lau, & Salzman, 2011). However, for the purpose of this introduction and its relevance to subsequent chapters the focus will be on the encoding, representation, and modulation of emotional cues in the amygdala.

1.2.3 Competing for representation

Within the brain there is a finite capacity for the representation of stimuli, which means not all information is processed to the extent that it can influence cognition or behaviour (Lavie, 2005). According to the biased-competition model (Desimone & Duncan, 1995), when two stimuli compete for representation within a given region they do so in a mutually inhibitory manner. The stimulus that "wins" and becomes preferentially represented is the one that is biased in at least one of two ways. It is biased in either a bottom-up fashion driven by stimulus properties (e.g., visual saliency such as a bright colour, or motion), or by processes initiated in regions of the frontoparietal cortices associated with executive attention or cognitive control (i.e., top-down processes). This has been demonstrated in both humans (Kastner, De Weerd, Desimone, & Ungerleider, 1998) and monkeys (Reynolds, Chelazzi, & Desimone, 1999) within the visual system. While the remainder of this section focuses on stimulus-driven (bottom-up) biased-competition and representation, the attention-related processes will be relevant to the later section on emotion control.

Emotion appears to be another form of saliency. Emotional significance enhances the neural representation of emotional stimuli in the amygdala and sensory regions (Pessoa, McKenna, Gutierrez, & Ungerleider, 2002; Vuilleumier, Armony, Driver, &

Dolan, 2001). In fact, it does so under conditions of both reduced attention to (Vuilleumier et al., 2001), and awareness of (Morris, Ohman, & Dolan, 1998), emotional stimuli. A critical question regarding emotional processing is how conflicting salient socio-emotional stimuli (i.e., faces) compete for neural representation. Our lab recently demonstrated that healthy participants are slower at judging a facial expression surrounded by competing facial expressions (Amting et al., 2009). Activity in the amygdala was observed in response to both happy and fearful faces. However, while amygdala activity to fearful faces was resilient to the impact of distracting faces, activity for happy faces was attenuated by competing facial expressions. These findings suggest that the social-emotional context can affect behavioural and neural representations of emotion, particularly positive emotions. An important unknown is how socio-emotional cues compete for representation in individuals with apparent emotional reactivity dysfunction or abnormal biases in information processing. For example, as will be discussed in a later section, individuals with MDD are often described as having a negative-bias, which may influence how emotional cues are represented.

1.3 Emotion control and its neural correlates

1.3.1 Defining emotion control

Emotion control can be operationally defined as the modulation of emotions when they are excessive or inappropriate. As represented in Figure 1.1, the control of emotions can be broadly conceived of as a continuum divided into components which are ‘reflexive’ at one extreme, and those which are ‘effortful’ at the other (Todd, Cunningham, Anderson, & Thompson, 2012). Of note, ‘reflexive’ is used here to represent those processes which are *not* (i.e., antithetical to) executed consciously and/or with effort, and does not necessarily imply reflexivity or automaticity in the strictest sense. In this manner, similar models of emotion regulation use the terms ‘automatic’ rather than ‘reflexive’, versus ‘voluntary’ rather than ‘effortful’ (Phillips, Ladouceur, & Drevets, 2008). Included in the more reflexive processes are learning mechanisms which

rely on phylogenetically older regions of the cortex (i.e., those which are largely agranular or dysgranular in their cytoarchitecture; Ray & Zald, 2012), including aspect of the caudal vmPFC. Discussions of reflexive emotion control will emphasize extinction learning, as it is a process which is well described in both the animal model and human literature. So as to avoid confusion with the ‘reflexive’ components of emotion control, the more ‘effortful’ components will be referred to as processes of emotion regulation (Ochsner & Gross, 2005). *Emotion regulation*, therefore, involves the effortful, voluntary, and intentional control of cognition and attention so as to modulate emotional reactivity. Emotion regulation can be further sub-divided into direct or indirect processes (Ochsner & Gross, 2005). The *direct* regulation of emotions involves processes of cognitive control, like cognitive reappraisal, or thought-stopping in which the emotional content of the stimulus is directly addressed or manipulated (Ochsner, Bunge, Gross, & Gabrieli, 2002; Ochsner et al., 2004). Conversely, *indirect* emotion regulation involves attention control and can be accomplished by engaging in non-emotional, cognitively demanding, or otherwise distracting tasks, which modulate the impact of emotions by focusing away from the emotional stimulus directly (Bishop et al., 2007; Mitchell et al., 2007; Pessoa et al., 2002). Both direct and indirect emotion regulation processes appear to engage regions of the lateral and dorsal prefrontal cortex implicated in cognitive control and executive attention. Refer to Figure 1.1 for a graphical representation of this framework for emotion control, which is referred to throughout the thesis.

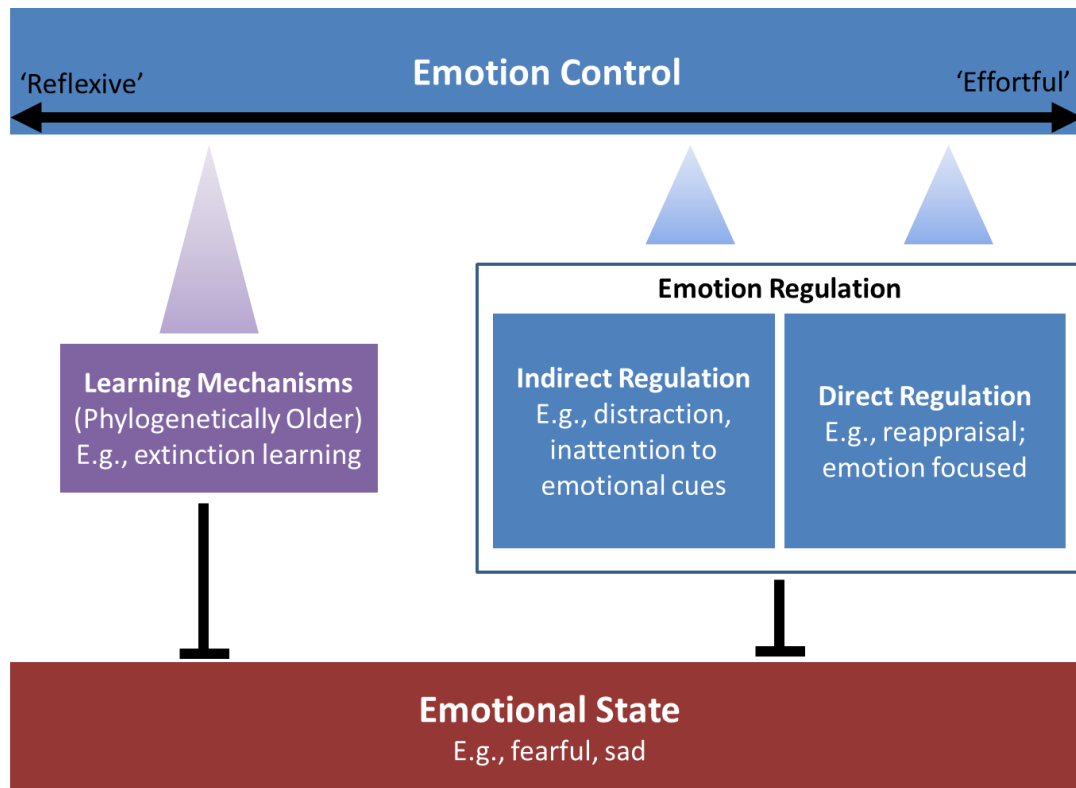


Figure 1.1 Schematic of the various sub-components of emotion control

This schematic demonstrates the various sub-components of emotion control and provides examples of how they work to inhibit, or modulate the impact of, emotional reactions.

1.3.2 Neurocognitive model of vmPFC function

One region often implicated in the 'reflexive' or 'automatic' control of emotional reactivity, and the direct modulation of amygdala reactivity, is the vmPFC. The vmPFC is most often associated with a mechanism called extinction learning, which is a Pavlovian process whereby a learned stimulus-reinforcement memory is inhibited when it is no longer valid (Milad & Quirk, 2012). Extinction learning is thought to be achieved primarily through the modulatory effects of vmPFC efferents on the intercalated cells of

the amygdala (see Figure 1.2), which inhibit activity in the amygdala's central nucleus (Milad & Quirk, 2002; Quirk, Likhtik, Pelletier, & Pare, 2003; Rosenkranz & Grace, 2002; Rosenkranz, Moore, & Grace, 2003). The vmPFC encodes a “safety” memory (i.e., the conditioned stimulus no longer signals threat) that competes with the fear memory in an inhibitory fashion, rather than erasing the original fear memory *per se* (Quirk, Garcia, & Gonzalez-Lima, 2006). Notably, most of the research delineating this functional pathway has involved the extinction of fear-conditioned responses in small mammals and emphasizes the infralimbic aspect of the ventromedial prefrontal cortex (Quirk et al., 2006). In humans, the medial prefrontal cortex broadly encompasses the anterior aspects of the medial wall of the prefrontal cortex from the frontal pole to regions anterior to the motor cortex. In the context of emotion control and the modulation of amygdala activity, the focus will largely be on the vmPFC. This includes Brodmann's areas (BA) 10/11/12, rostral anterior cingulate (rACC; BA 24/32/33) and subgenual prefrontal cortex (sgPFC; BA 25 and parts of BA 24/32/33) which combine to form the perigenual prefrontal cortex (pgPFC), and medial aspects of the orbitofrontal cortex (mOFC, BA 11/12). Although the cytoarchitecture of the rodent infralimbic region and the human vmPFC differ markedly (Ray & Zald, 2012), human imaging studies of the extinction of fear learning (Milad et al., 2007; Phelps, Delgado, Nearing, & LeDoux, 2004) and others on fear-related emotion suppression (Amtong, Greening, & Mitchell, 2010) have corroborated the role of vmPFC in the modulation of fear. However, studies examining the role of the vmPFC in the modulation of more complex human emotions suggest that it does more than extinguish fear. During instrumental learning the vmPFC seems to encode the reward value associated with a target stimulus and/or a specific behavioural response (Boorman, Behrens, Woolrich, & Rushworth, 2009; Tanaka, Balleine, & O'Doherty, 2008). Lesion studies have found the vmPFC is necessary for flexibly adapting to changing stimulus-value contingencies (e.g., stimulus ‘A’ switches from being associated with a reward to being associated with a punishment), but not for learning the initial stimulus-value relationship (Fellows & Farah, 2003). It is also activated by certain self-referential processes (Bluhm et al., 2012), including imagination (Schacter et al., 2012), though these processes have also been found in more dorsal regions of the medial prefrontal cortex (Frewen et al., 2011). A recent review has suggested that the vmPFC may be more

generally associated with the ‘generation of affective [or emotional] meaning’ (Roy, Shohamy, & Wager, 2012). Nevertheless, the many studies of extinction learning have provided a comprehensive understanding of the neural circuitry whereby the vmPFC can modulate amygdala reactivity in various emotional contexts.

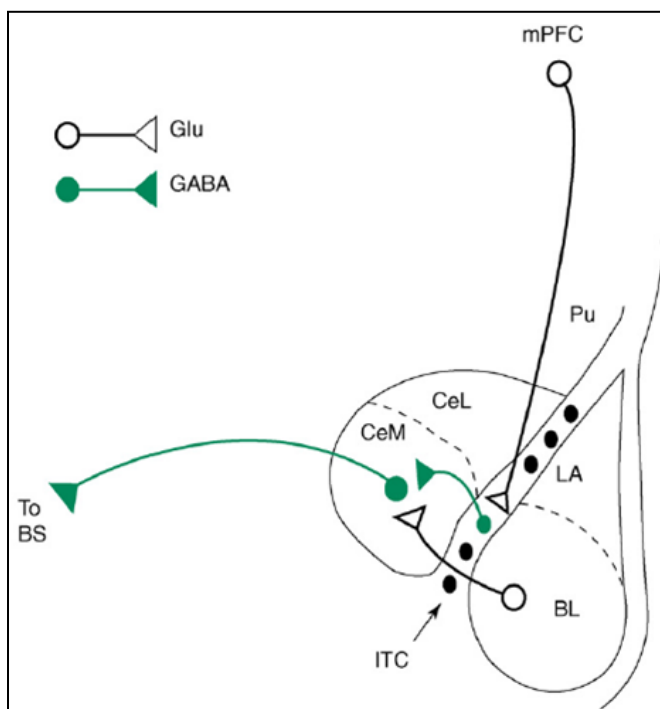


Figure 1.2 Neurobiological mechanisms of extinction learning

This figure highlights the excitatory inputs of the medial prefrontal cortex (mPFC) on intercalated neurons (ITC) of the amygdala. The ITC neurons are inhibitory (GABAergic) neurons that project to the central nucleus (CeM) of the amygdala and modulate its output. Conversely, projections to the CeM from the basolateral (BL) amygdala are excitatory in nature. The BL is involved in processes of emotional (e.g., fear) learning. The CeM projects to brainstem (BS) related structures, which are involved in the production of fear-related responses. This figure is printed with permission from Bishop (2007).

1.3.3 Direct and indirect effortful emotion regulation

The effortful regulation of emotion, whether direct or indirect, consistently implicates dorsal regions of prefrontal cortex. These include both the dlPFC and the dmPFC (see Figure 1.3 for a graphical representation of these processes). Anatomically, the dlPFC includes parts of the middle and superior frontal gyri, including BA 8/9/46. The dmPFC includes the medial wall of the prefrontal cortex above the cingulate gyrus, including BA 8/9. While the dlPFC is most often associated with voluntary or executive attention (Corbetta & Shulman, 2002; Kastner & Ungerleider, 2000), the dmPFC is associated with conflict monitoring (Botvinick, Cohen, & Carter, 2004). However, favoured models of general cognitive control emphasize the complimentary interactions between dlPFC and dmPFC (Duncan, 2010; Duncan & Owen, 2000), as do models regarding the cognitive control of emotions specifically (Bishop, 2007; Blair & Mitchell, 2009). During the reappraisal and subsequent down-regulation of negative emotions there is enhanced activity in either or both the dlPFC and the dmPFC (Goldin, McRae, Ramel, & Gross, 2008; Ochsner et al., 2002; Ochsner et al., 2004; Phan et al., 2005). Similar activity is observed in these regions during indirect emotion regulation tasks using manipulations of attention or cognitive load (Bishop, Duncan, Brett, & Lawrence, 2004; Bishop et al., 2007; Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010; Mitchell et al., 2007). Furthermore, in two studies comparing distraction and reappraisal there was striking overlap in regions of dlPFC and dmPFC (Kanske, Heissler, Schonfelder, Bongers, & Wessa, 2011; McRae et al., 2010). In the majority of these studies there were also concurrent reductions in amygdala activity.

In terms of the neural mechanism responsible for the modulation of emotional reactions by the dorsal prefrontal regions, there are a number of theories. Some suggest that, consistent with the role of voluntary attention in the biased competition model, emotion regulation works by augmenting stimulus representations that inhibit the representations of unwanted or distracting emotions (Bishop, 2007; Blair & Mitchell, 2009; Mitchell, 2011). It is speculated that dlPFC and related cognitive control structures inhibit amygdala activity indirectly by way of the occipitotemporal cortices involved in the representation of sensory information. Specifically, dlPFC is thought to stabilize the

representation of non-emotional task relevant stimuli in occipitotemporal cortex, which through competitive processes reduces representation of emotional distracters (see Figure 1.3). In this way processing resources are prioritized to goal relevant stimuli. However, alternative explanations have been made regarding the modulation of the amygdala by dlPFC. Often, vmPFC activity is also observed during effortful emotion regulation, which has led some to suggest that dlPFC acts by virtue of connections with the vmPFC (Delgado, Nearing, Ledoux, & Phelps, 2008). Nevertheless, the precise role of dlPFC and dmPFC in emotion regulation remains a matter of debate. It is important to note that much of the research delineating the role of these regions in emotion regulation has involved negative emotions. Far fewer studies have considered the regulation of positive emotions (Ochsner, Silvers, & Buhle, 2012). Although similar findings have been reported in both dlPFC and dmPFC (Kim & Hamann, 2007), one other study found enhanced coupling between NAcc and dlPFC during the up-regulation of positive emotions (Heller et al., 2009). Additionally, no study to date has directly compared enhancing positive to reducing negative emotions to assess differences in the regions required for the two processes. Although there is an emerging understanding of how attention and cognitive control regions are involved in emotion regulation, there remain a number of unknowns. Few studies have investigated how regions of dlPFC and dmPFC respond during emotion regulation in patients with disorders of emotion, like depression.

1.3.4 The vlPFC and emotion control

Early conceptions of the vlPFC indicated that it is involved in directing attention (Corbetta & Shulman, 2002). This region also responds more robustly when task-relevant, but non-salient objects are presented (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010; Hampshire & Owen, 2006), which suggests its activity is modulated by effortful cognitive processes such as goals. Earlier work demonstrated that the vlPFC is necessary for motor response inhibition during a reactive stopping paradigm (Aron, Robbins, & Poldrack, 2004). More recently, research has found that the vlPFC is more generally involved when stimulus-response-reward associations change (Greening, Finger, & Mitchell, 2011; Mitchell et al., 2009; Nagahama et al., 2001). Most relevant to

the current thesis, other research has demonstrated that vIPFC is involved in more complex, effortful, emotion regulation tasks such as cognitive reappraisal (Johnstone et al., 2007; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008). Thus, the vIPFC appears to be involved in effortful emotion regulation. The area of vIPFC generally encompasses parts of the inferior frontal gyrus (IFG; BA 47, and parts of 11/44/45), including anterior aspects frontal operculum, as well as the pars opercularis, pars triangularis, rostral aspects of pars orbitalis (Aron, 2011).

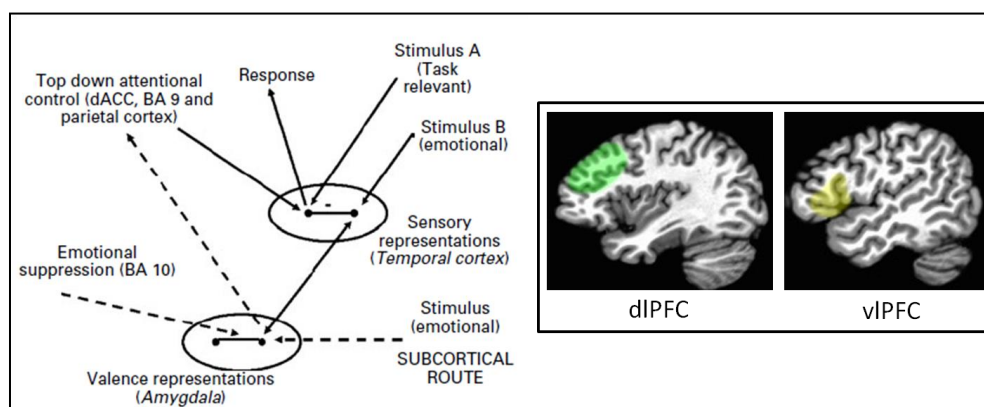


Figure 1.3 A model of the brain regions implicated in emotion regulation

Left - A model demonstrating how top-down attention might modulate emotional reactivity, reprinted with permission from Blair and Mitchell (2009). Attention-related connections from regions of the frontoparietal cortex, including dlPFC, dmPFC, and vIPFC (though not mentioned in the figure) activate task-relevant (Stimulus A) representations in the sensory cortex. This activation of task-relevant representations inhibits the representation of emotional task-irrelevant stimulus representations in sensory cortices (via the processes of biased-competition). This inhibition of emotional representation in the sensory cortices also has the effect of inhibiting emotional representations in the amygdala, possibly due to disrupted feedback between the amygdala-cortical connections needed to sustain amygdala activity. Right - anatomical depiction of the dlPFC (green) and the vIPFC (yellow).

1.4 Depression and emotional (in)flexibility

The study of psychiatric disorders (e.g., MDD), using a neurocognitive approach is beneficial for at least two reasons. First, it provides insight into the interaction between cognitive and biological processes involved in the disorder, and can be used for improving clinically-related aspects of the disorder (e.g., treatment development and evaluation). Second, the study of psychiatric populations can provide insight into the underlying neurocognitive substrates of a given process or behaviour. This section will begin with a description of the clinical features and cognitive theories of MDD, followed by a discussion of the previous research into the neurobiological basis of the disorder. The final two part of this section will integrate the discussion of cognitive and neurobiological features of MDD by considering studies that have investigated the functional correlates of MDD using a neurocognitive approach.

1.4.1 Clinical features

Roughly one in ten Canadians will suffer from major depressive disorder (MDD) in their lifetime (Stewart et al., 2006; Stewart, Lips, Lakaski, & Upshall, 2002). The annual economic burden of mental disorders in Canada is estimated to be greater than six billion dollars (Stewart et al., 2006). Yet current therapies for mood disorders are associated with low remission (25-50%) (Trivedi et al., 2006) and high relapse rates (over 50%) (Rush et al., 2006; Vittengl, Clark, Dunn, & Jarrett, 2007), and current antidepressant medications are often associated with a number of adverse side-effects (Thase et al., 2007). The Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000) defines a major depressive episode as the presentation of at least five of the following symptoms for at least a two week period, with either one or both of the first two symptoms (core features) necessarily present: 1) depressed mood; 2) lack of interest or pleasure; 3) significant weight loss or gain; 4) insomnia or hypersomnia nearly every day; 5) psychomotor agitation or retardation; 6) fatigue or loss of energy; 7) feelings of worthlessness or inappropriate guilt; 8)

diminished ability to think or concentrate, or indecisiveness; and 9) thoughts of suicide. An individual diagnosed with major depressive disorder has experienced the occurrence of at least one major depressive episode.

MDD, along with anxiety disorders, are often considered to be disorders of emotion (Barlow, 1991; Campbell-Sills & Barlow, 2007; Davidson, Pizzagalli, Nitschke, & Putnam, 2002). For example, dysfunctional emotional reactivity and impaired emotion regulation are both observed in MDD and are both targets for treatment (Davidson et al., 2002). It should also be noted that depression shares a high rate of comorbidity with anxiety (Kessler, Chiu, Demler, Merikangas, & Walters, 2005). Relevant to the discussion of emotional reactivity, it has been suggested that there is a core feature shared across both disorders, namely negative emotional reactivity, though the disorders are assuredly distinct (Barlow, 1991). Furthermore, there is evidence to suggest that high trait-anxiety is a risk factor for developing MDD (Cole, Peeke, Martin, Truglio, & Seroczynski, 1998), in addition to disorders of anxiety.

1.4.2 Cognitive theories of depression

There are at least two prevailing cognitive theories regarding emotional reactivity in MDD. Negative-bias theories of depression predict that negative information (Beck, Rush, Shaw, & Emery, 1979) is preferentially processed at all levels of cognition, and that this bias plays a key role in initiating and maintaining depressed moods. Supporting this hypothesis, depression is associated with enhanced processing of negative stimuli in terms of explicit memory (Bradley, Mogg, & Williams, 1995; Mogg, Bradbury, & Bradley, 2006), perseverative attention towards negative cues (Bradley, Mogg, & Lee, 1997; Leyman, De Raedt, Schacht, & Koster, 2007), and working memory (Levens & Gotlib, 2010). Functional imaging studies have also found that amygdala activity can be greater for negative emotional cues in depressed relative to control participants (Fu et al., 2004; Sheline et al., 2001). However, the empirical picture is complex. Although the negative-bias theory predicts that biases should be evident at all levels of information processing (i.e., at early as well as late levels of processing), studies that target rapid

shifts of attention often fail to show evidence of a bias towards negative stimuli (Bradley et al., 1997; De Raedt & Koster, 2010; Mogg, Millar, & Bradley, 2000). Furthermore, empirical evidence suggests that deficient reactivity to salient socio-emotional stimuli is associated with depression (Surguladze et al., 2004) and depression vulnerability (Elliott et al., 2012).

Recently, an alternative cognitive theory has been proposed to account for the blunted affect often observed in patients with MDD. The emotional context insensitivity (ECI) theory posits that MDD is associated with attenuated emotional reactivity to both positive and negative cues (Morris et al., 2009). This theory is supported by considerable experimental evidence (Dawson, Schell, & Catania, 1977; Rottenberg, Gross, & Gotlib, 2005; Rottenberg, Kasch, Gross, & Gotlib, 2002). For example, a recent meta-analysis demonstrated that both positive and negative affect was blunted in MDD across multiple indices of emotional reactivity (Bylsma, Morris, & Rottenberg, 2008). The focus of the meta-analysis was on self-reported measures of emotional reactivity and peripheral physiology. The degree to which ECI is observed at the neural level remains unclear.

Given conflicting evidence for both the negative-bias and ECI theories, and the importance of emotional reactivity for depression prognosis, a better understanding of the factors that determine how depressed individuals react to emotional cues is critical. One suggestion has been that heterogeneity within the disorder leads to the conflicting results (Fournier et al., 2012). However, another non-mutually exclusive possibility is that reactivity may vary within patients depending on the behavioural context, and that the level of attention deployed may be a key determinant of whether an affective bias or insensitivity arises. For example, there is some evidence that negative-biases are absent at shorter intervals, yet they are observed if emotional distracters are presented at longer durations (Joormann & Gotlib, 2007; Leyman et al., 2007). This raises the possibility that task-demands (e.g., attention) need to be considered when studying emotional processing, including emotional reactivity and emotion control, in individuals with MDD.

1.4.3 Neurobiological basis of depression

Seminal work into the neurobiological basis of depression involved the measurement of cerebral blood flow (or metabolism) using positron emission tomography (PET) at rest in patients with MDD. Using this approach Drevets et al. (1992) demonstrated that the amygdala had increased cerebral blood flow during both a major depressive episode and during symptom remission, though the latter was a trend towards significance. This suggests that heightened amygdala activity may be related to both state (i.e, it is present during a depressive episode) and trait (i.e., it persists during symptom remission and may be a risk factor for the disorder) components of MDD. Furthermore, amygdala blood flow during a depressive episode has been positively correlated with depression severity (Abercrombie et al., 1998; Drevets et al., 1992). In addition, studies of post-mortem brain tissue have found reduced glial density in the amygdala (Bowley, Drevets, Ongur, & Price, 2002), which is consistent with human imaging findings of reduced amygdala volume (Sheline, Gado, & Price, 1998; Tang, Wang, et al., 2007). Thus, along with evidence from studies of emotional reactivity, these findings have led to the amygdala being identified in most neurobiological models of depression as an important locus of dysfunction.

The vmPFC, in particular the subgenual prefrontal cortex (BA 24/25), has also been consistently implicated in MDD. Most consistent are observations of hyper-metabolism at rest in subgenual regions of vmPFC during depressive episodes (Mah et al., 2007; Mayberg et al., 2000), which improves with selective-serotonin reuptake inhibitor (SSRI) antidepressant treatment (Mayberg et al., 2000). Additionally, anatomical studies have revealed reduced glial density (Ongur, Drevets, & Price, 1998), and reduced structural volume (Drevets et al., 1997) in aspects of the vmPFC. Deep brain stimulation of this region in patients with treatment resistant depression has also been shown to significantly improve symptoms of depression (Mayberg et al., 2005). A recent study of Vietnam War veterans also demonstrated that lesions to vmPFC were protective against depression and also anxiety (Koenigs, Huey, Calamia, et al., 2008; Koenigs, Huey, Raymont, et al., 2008). Furthermore, there are two intriguing cases in which an individual suffering from MDD has attempted suicide but instead ended up destroying the

bilateral vmPFC while leaving the lateral PFC intact (Ellenbogen, Hurford, Liebeskind, Neimark, & Weiss, 2005; Koenigs & Grafman, 2009). In both cases, following the trauma both the patients and third-party feedback reported markedly reduced depressive symptoms to the point of apparent remission.

Similar neurobiological research has found differences in brain regions associated with emotion regulation, including the lateral and dorsal prefrontal cortex. Reduced numbers of glial cells and neurons has been observed in the dlPFC of patients with MDD (Rajkowska et al., 1999), as has reduced grey matter volume (Salvadore et al., 2011). Similarly, reduced neuron density has been found in parts of the vlPFC (Rajkowska et al., 1999). MDD also appears associated with hypo-metabolism in dlPFC (Mayberg, 2002). Although hyper-metabolism has been observed in vlPFC of patients with MDD, the activity appears negatively correlated with depression severity. Interestingly, successful MDD treatment with cognitive behaviour therapy (CBT) was associated with reduced activity in vlPFC, dlPFC, and dmPFC (Goldapple et al., 2004). Finally, Vietnam War veterans with lesions to superior aspects of the dlPFC had a significantly elevated risk for developing depression (Koenigs, Huey, Calamia, et al., 2008).

Importantly, although the work described above has provided great insight into the neurobiological basis of MDD, it does not provide insight into the functional contributions of these brain regions during emotional processing. Thus, these studies do not allow for inferences regarding how these brain regions operate or interact during instances of emotional reactivity or emotion control.

1.4.4 Depression, emotional reactivity, and the amygdala

One important facet of dysfunctional emotional reactivity in MDD involves compromised socio-emotional processing (Paykel, 2002; Schelde, 1998; Surguladze et al., 2004). Much of the functional neuroimaging literature of emotional reactivity has focused on the amygdala and its response to socio-emotional cues including facial expressions. Heightened activity in the amygdala in response to negative cues (e.g., sad

or fearful faces) is often reported in depression (Fu et al., 2004; Sheline et al., 2001; Surguladze et al., 2005), which seems to resolve following treatment with antidepressants (Sheline et al., 2001; Victor, Furey, Fromm, Ohman, & Drevets, 2010). However, results from other studies utilizing negative cues have revealed heterogeneous results, including reduced (Fales et al., 2008; Lawrence et al., 2004; Ritchey, Dolcos, Eddington, Strauman, & Cabeza, 2011), as well as normal (Almeida, Versace, Hassel, Kupfer, & Phillips, 2010; Keedwell, Andrew, Williams, Brammer, & Phillips, 2005) emotional reactivity in depressed patients.

Studies have also demonstrated that MDD is associated with reduced amygdala responsiveness to positive (e.g., happy) expressions, and depression severity is negatively related with the amygdala's response to such stimuli (Suslow et al., 2010). It has been suggested that between-sample heterogeneity may account for discrepant findings regarding amygdala reactivity to negative socio-emotional cues. For example, MDD patients who are homozygous for the short allele of the serotonin receptor-transporter gene thought to be a risk-factor for depression display greater amygdala reactivity to negative facial expressions (Dannlowski et al., 2008). In another example, those patients with a greater degree of sub-threshold mania have greater amygdala activity to happy faces (Fournier et al., 2012). An additional and important possibility is that task demands, such as the socio-emotional context of a task, can have a distinct influence on how emotions are processed in the amygdala of individuals with MDD. For example, differential amygdala reactivity has been shown in a task in which basic socio-emotional signals compete for neural representation (i.e., when a participant has to identify a fearful face surrounded by peripheral and distracting happy faces, Amting et al., 2009). In patients with MDD we might predict that regardless of whether negative faces are centrally presented and task-relevant, or whether they are peripheral distracters, the amygdala would respond preferentially to those negative cues (i.e., in a manner consistent with a negative-bias). Alternatively, consistent with tasks demonstrating that the performance of basic non-emotional tasks can reduce the amygdala's response to distracting fearful facial expressions in healthy participants (Mitchell et al., 2007; Pessoa et al., 2002), we might predict that a central socio-emotional task reduces the impact of distracting negative cues in MDD. In other words, the behavioural context might affect

amygdala reactivity such that there is reduction in activity in both MDD and control participants when the negative cues are task-irrelevant. Thus, given the research reviewed in this and the previous paragraph an important question regarding socio-emotional processing in patients with MDD is: How are conflicting basic socio-emotional cues integrated within the brain, and within the amygdala more specifically, of individuals with MDD? This topic is the main focus of Study 1 (Chapter 2).

1.4.5 Emotion modulation and vmPFC in depression

Regarding the vmPFC and emotion modulation in depression, there are few studies reporting on the subgenual aspects of the prefrontal cortex. This is assumed to be largely due to the signal drop-out that occurs in this region using the echoplanar imaging parameters common to fMRI (Devlin et al., 2000). Nevertheless, other regions of vmPFC have been observed. For example, abnormally reduced activity in vmPFC to both happy and sad task-relevant cues has been observed in MDD patients (Elliott, Rubinsztein, Sahakian, & Dolan, 2002), which might suggest this region is unresponsive during situations in which reflexive emotion control is normally observed. In another study, during attempts to reappraise negative stimuli MDD patients displayed enhanced vmPFC along with enhanced amygdala activity, whereas controls demonstrated enhanced vmPFC with reduced amygdala activity (Johnstone et al., 2007). In a resting-state study using a similar paradigm, Sheline et al. observed persistently elevated vmPFC during both the passive viewing and reappraisal of negative stimuli along with heightened amygdala reactivity (Sheline et al., 2009). Functional connections from the vmPFC to the amygdala were also impaired in both depressed and bipolar-depressed patients during the viewing of happy faces, and a similar trend was observed for sad faces (Almeida et al., 2009). These studies appear indicative of dysfunction in vmPFC during the control of either positive or negative emotions, which is also related to abnormal functional connectivity with the amygdala.

1.4.6 Emotion regulation: reappraisal and attention in depression

The use of cognitive therapy, or cognitive behaviour therapy, has proven to be as effective at treating MDD as antidepressant medication (DeRubeis, Gelfand, Tang, & Simons, 1999; Thase et al., 2007), though it is associated with fewer adverse side-effects (Thase et al., 2007). Moreover, there appears to be a significant proportion, roughly 25% or more, of MDD patients who respond within one session of CBT (Tang, Derubeis, Hollon, Amsterdam, & Shelton, 2007a). The research reviewed in the previous section, which implicated the dlPFC, dmPFC, and vlPFC in MDD, employed resting-state brain imaging. This approach does not provide information regarding the functional recruitment of these regions during specific tasks. Prospective studies examining the functional neural response to negative emotional cues pre- and post-CBT have demonstrated enhanced functional activity in regions of dlPFC and dmPFC, along with reduced amygdala activity (DeRubeis, Siegle, & Hollon, 2008; Fu et al., 2008). However, these studies did not examine the functional changes in these regions while participants explicitly engaged in direct emotion regulation.

To date, a number of studies have attempted to determine the nature of dysfunction in regions of the dlPFC, dmPFC, and vlPFC associated specifically with direct emotion regulation (e.g., reappraisal) in MDD. However, the results have been inconsistent. Regarding the regulation of negative emotions, research into the neural correlates of down-regulating negative emotions has been somewhat mixed. Johnstone et al. (2007) found that MDD and control participants had increased activity in vlPFC; however, MDD and not control participants had increased activity in dlPFC during attempts to down-regulate negative emotions. Furthermore, Johnstone et al. (2007) did not find between-group differences in amygdala activity, though a follow-up analysis demonstrated that the down-regulation of amygdala activity was functionally mediated by a pathway from vlPFC to vmPFC in controls but not depressed participants. Conversely, Erk et al. (2010) found that while amygdala reactivity decreased in MDD patients in a manner negatively correlated with depression severity (i.e., less severity was associated with greater amygdala attenuation), MDD patients displayed significantly less activity in the dlPFC relative to controls during the down-regulation of negative emotions. In terms

of the direct up-regulation, or enhancement, of positive emotions, there is only one study to date. Heller et al. (2009) observed reduced functional connectivity between the dlPFC and NAcc during the second half of positive up-regulation trials in MDD but not control subjects (i.e., controls had robust functional connectivity in the first and second half of the experiment). Moreover, those MDD patients with greatest dlPFC-NAcc functional connectivity demonstrated the greatest increase in positive emotionality following two months of treatment with antidepressants. Remarkably, none of the above studies measured emotional reactivity to the stimuli during the scan. In addition, the reappraisal strategies that have been used in fMRI studies of MDD do not necessarily resemble those used in treating MDD (e.g., CBT). For example, while some have had participants imagine that the scene being observed is fake or unreal (Heller et al., 2009; Johnstone et al., 2007), others ask participants to adopt the perspective of a detached observer (Beauregard, Paquette, & Levesque, 2006; Erk et al., 2010). This is potentially critical given that different regulation strategies can recruit distinct neural mechanisms (Goldin et al., 2008; Ochsner et al., 2004). Furthermore, the majority examined only prefrontal cortical regions (using a prefrontal cortex mask) along with the amygdala and NAcc, though Erk et al. (2010) are the exception. So as to address these limitations, Study 2 (Chapter 3) of the current thesis used a reappraisal strategy derived from CBT to examine the neural correlates of both negative and positive emotion regulation.

Regarding indirect emotion regulation (i.e., the modulation of emotion by engaging in a non-emotional cognitive task), reduced dlPFC activity appears associated with elevated amygdala activity in response to negative stimuli in MDD relative to control participants (Fales et al., 2008; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007). This appears to suggest that the dlPFC of individuals with MDD, which is important for emotion regulation in general (i.e., both direct and indirect forms), is ineffectual at modulating neural activity in regions associated with emotional reactivity during indirect emotion regulation. Together with the previous paragraph, the precise neurocognitive basis of emotional impairments remains enigmatic with regards to MDD and neurocognitive models of emotion regulation. However, the combination of functional neuroimaging with cognitive tasks that manipulate the context of emotional processing holds promise for further delineating the neurocognitive impairments associated with

depression. Both Study 1 (chapter 2) and Study 2 (chapter 3) are aimed at addressing this need.

1.5 Structural connectivity and emotional flexibility

Neither the amygdala nor the regions implicated in emotional flexibility are likely to be acting in isolation to facilitate emotional flexibility or to produce the abnormalities associated with emotional disorders. Studies of functional connectivity have provided some insight into functional interactions between regions associated with emotional representation and modulation. For example, in a recent study by Amting, Greening, and Mitchell (2010), awareness of fearful faces was associated with positive functional connectivity between the amygdala and regions of the extrastriate cortex involved in visual perception. Conversely, when fearful faces were suppressed from awareness there was negative functional connectivity between the amygdala and the vmPFC. This is consistent with findings from others who have demonstrated a similar pattern of connectivity is associated with individual differences in trait-anxiety. For example, Dunsmoor et al. (Dunsmoor, Prince, Murty, Kragel, & LaBar, 2011) demonstrate that increased functional connectivity between the amygdala and extrastriate cortex during fear-generalization was positively correlated to trait-anxiety. On the other hand, during contextual fear conditioning trait-anxiety was positively correlated with amygdala activity but negatively correlated with vmPFC activity (Indovina, Robbins, Nunez-Elizalde, Dunn, & Bishop, 2011). Furthermore, the magnitude of negative functional connectivity between the amygdala and regions of the vmPFC and dlPFC appears positively associated with the reduction of negative emotions (Banks, Eddy, Angstadt, Nathan, & Phan, 2007). However, functional connectivity does not allow for strong inferences regarding the structural connectivity between regions to be drawn. Diffusion-weighted imaging (DWI) is a technique that measures the diffusion of water molecules in various directions in a given brain voxel (i.e., a volumetric, or 3-dimensional, pixel), and thus can be used to assess structural connectivity within the brain. As with functional

studies, we can begin to identify the structural connections that contribute to flexible emotional adaptation by considering both between group studies and studies examining individual differences in personality traits that relate to emotional reactivity. The between group studies will consider patients with various emotional disorders, with an emphasis on depression.

1.5.1 Between group differences in measures of white-matter

To date, much evidence regarding white-matter differences related to emotional reactivity or emotion control comes from studies comparing patients (e.g., individuals with mood or anxiety disorders) to healthy controls. Along with standard whole-brain or region-of-interest masking procedures to perform direct analysis of functional anisotropy (FA; i.e., a measure of white-matter microstructure integrity) differences, a common method used for these between group designs is a technique called tract-based spatial statistics (Smith et al., 2006). Briefly, a standardized white-matter skeleton is created along the major white-matter tracts (see Figure 1.4), which allows for the comparison of FA across groups from the images of each participant. The major strength of this approach is that it can be used to perform whole-brain style analyses similar to those used in fMRI (Smith et al., 2006; Smith et al., 2007). Consistent with the role of the vmPFC in the modulation of the amygdala, FA appears reduced (i.e., abnormal or impaired) within regions associated with the uncinate fasciculus in a number of emotional disorders, including adults and youth with MDD (Cullen et al., 2010; Nobuhara et al., 2006), bipolar disorder (Versace et al., 2008), generalized anxiety disorder (Hetttema et al., 2012), and social anxiety disorder (Baur et al., 2011; Phan et al., 2009). The uncinate fasciculus is a major white-matter tract that connects the anterior temporal lobe, including the amygdala, to ventral aspects of the prefrontal cortex, including the vmPFC. Regarding regions implicated in emotion regulation, similar reductions in FA have been observed in the superior and inferior longitudinal fasciculi in MDD (Korgaonkar et al., 2011; Murphy & Frodl, 2011; Versace et al., 2010), bipolar (Versace et al., 2010), and anxiety disorders (Baur et al., 2011). While the superior longitudinal fasciculus is a large white-matter bundle connecting lateral prefrontal cortex to parietal regions and extends

into the superior temporal gyrus, the inferior longitudinal fasciculus is relatively smaller, connecting occipital and temporal lobes. It is, therefore, apparent that in disorders of emotion there are abnormalities in regions associated with both the reflexive and effortful control of emotion. However, an important caveat to this approach is that it is not possible to infer which fiber tracts, or inter-regional pathways, are specifically contributing to the observed difference (Smith et al., 2007). In other words, it is unclear whether these white-matter abnormalities exist within pathways connecting to the amygdala directly or indirectly, or whether these are pathways not at all related to the amygdala.

The second approach for examining DWI data involves seed-based probabilistic tractography (see Figure 1.4). In this approach, connections between a seed region and a target region are identified based on the likelihood that the two areas are structurally connected (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007). There are at least two ways to analyze DWI data using this approach. The first involves identifying all potential tracts connecting the seed and target regions, and then using those tracts as a mask to extract FA values. This approach has been used to identify parts of the uncinate fasciculus connecting to the amygdala and has revealed reduced FA in individuals with MDD (Cullen et al., 2010; Kwaastieniet et al., 2013; Zhang et al., 2012) and anxiety (Tromp et al., 2012), and interestingly also in individuals with psychopathy (Motzkin, Newman, Kiehl, & Koenigs, 2011). To date, there do not appear to be any seed-based connectivity studies which have considered regions associated with emotion regulation in MDD, though reduced FA in an inter-hemispheric pathway connecting the bilateral dIPFC, through the genu of the corpus callosum, has been found in individuals with social anxiety (Liao et al., 2011). The second way of using probabilistic tractography involves the use of the values that are directly output from the tractography process. These values include the estimated likelihood (a percentage, or a value between 0 and 1) that a given voxel in a seed region is connected to a given target regions. The use of this approach has only been used more recently, and was first used to perform anatomical segmentations of deep brain structures like the thalamus (Behrens et al., 2003), and amygdala (Bach, Behrens, Garrido, Weiskopf, & Dolan, 2011; Saygin et al., 2012). More recently, the strength of this approach was highlighted when Saygin et al. (Saygin et al.,

2012) demonstrated that probabilistic tractography estimates for voxels in the fusiform gyrus, to multiple targets throughout the brain, could be used to predict BOLD activity in response to faces. This potentially powerful approach appears to offer the ability to determine the relative contribution of multiple seed-target pathways and their relationship to individual differences in emotion processing, however no such study has been undertaken to date.

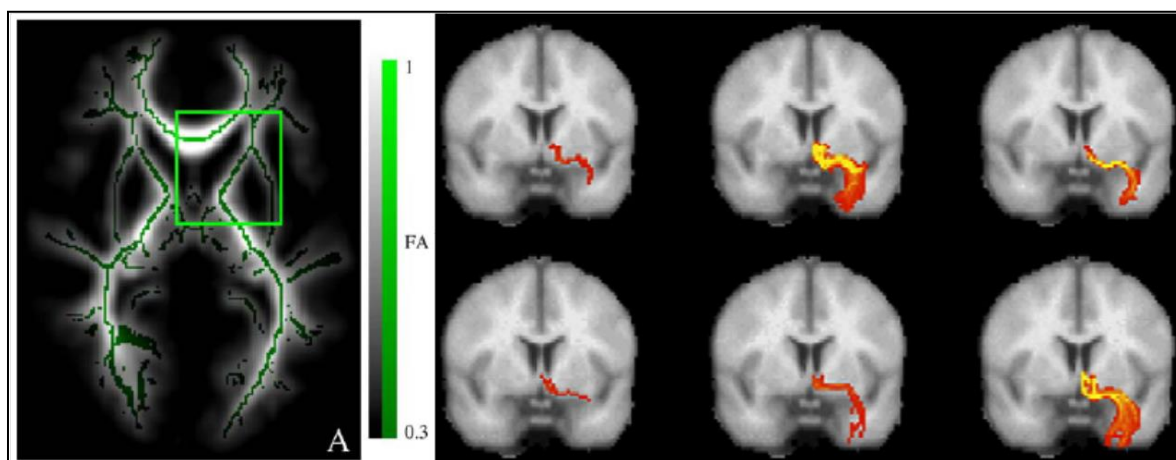


Figure 1.4 Depiction of the white-matter skeleton and probabilistic tractography approaches

Left - This figure depicts the white-matter skeleton produced using tract-based spatial statistics. After producing the skeleton, FA magnitude can be used to perform the type of whole-brain, between group, univariate analyses traditional to neuroimaging. This figure is printed with permission from Smith et al. (2006). Right - This figure depicts a pathway derived using probabilistic tractography in six coronal sections. This approach can be used to produce a mask from which FA can be extracted, or can be used to compute the likelihood or probability that two

disparate regions are structurally connected. This figure is printed with permission from Behrens et al. (2007)

1.5.2 Individual differences approach to structural connectivity

The use of individual differences analyses whereby brain-related measures (e.g., fMRI, DWI) are correlated with personality trait measures of emotional reactivity (e.g., Bishop et al., 2004), or examined using median splits of a participant sample (e.g., Bishop et al., 2007; Han et al., 2012), have proven extremely valuable. One reason for the utility of this approach is that it can be done using healthy participants, which are easier to recruit than patient samples. This also allows for the exclusion of participants with a history that may affect the structures of the brain, for example the use of antidepressant medication (Harmer, Goodwin, & Cowen, 2009). One such personality measure is trait-anxiety. As previously mentioned, not only is trait-anxiety associated with anxiety disorders, high trait-anxiety is a risk factor for the development of other emotion disorders, such as MDD (Cole et al., 1998). Indeed, scales of trait-anxiety are highly correlated with measures of individual differences in depression (Barlow, 1991; Gotlib, 1984). It has been suggested that this relationship is due to the fact that these personality measures are significantly influenced by individual differences in negative emotional reactivity (Barlow, 1991; Brown, Chorpita, & Barlow, 1998). Importantly, trait-anxiety has been used prolifically in functional neuroimaging studies of emotion to provide further insight into the brain mechanisms involved in flexible emotional responding (Basten, Stelzel, & Fiebach, 2011; Bishop et al., 2004; Bishop, 2009; Bishop et al., 2007; Fakra et al., 2009; Indovina et al., 2011).

Westlye et al. (Westlye, Bjornebekk, Grydeland, Fjell, & Walhovd, 2011) used tract-based spatial statistics in a large multi-cohort study to demonstrate that harm avoidance, a personality trait related to anxiety, was negatively correlated with FA throughout a large extent of the white-matter skeleton (~40%). More specifically, a highly anxious temperament was related to reduced FA in regions putatively corresponding to bilateral uncinate fasciculus, and superior and inferior longitudinal

fasciculi. On the other hand, Kim and Whalen (Kim & Whalen, 2009) identified a region-of-interest in the left hemisphere, proximal to putative uncinate fasciculus, in which BOLD activity to fearful faces was correlated with FA. They found that, within this region-of-interest, FA was also negatively correlated with trait-anxiety. Importantly, neither of these approaches assayed amygdala connectivity per se (i.e., they did not use probabilistic tractography). Thus we are unable to infer from these studies if amygdala connections specifically influenced individual differences of emotional reactivity (i.e., trait-anxiety). The seed-based probabilistic approach described in the previous section is one means to address this limitation. Moreover, the use of an approach similar to Saygin et al. (2012) could be used to determine whether an amygdala-centric network of connections contains sufficient information to predict individual differences in trait-anxiety. Study 3 of the current thesis (Chapter 4) was designed in this manner.

1.6 Overall thesis objective and hypothesis

The **overall goal** of this thesis is to investigate the functional and structural neural correlates of emotional flexibility, which includes facets of emotional reactivity and emotion control. The three studies introduced below represent a multi-faceted approach to studying both the functional and structural neural correlates of emotional flexibility. The **central hypothesis** is that emotional flexibility involves differential neural responses in regions involved in emotional reactivity and the control of negative and positive emotional responses. Furthermore, it is predicted that the processes of emotional flexibility are abnormal in individuals with an emotional disorder (i.e., MDD). Finally, it is predicted that the structural connectivity pattern between these brain regions reflects individual differences in emotional reactivity and emotion regulation, which emphasizes the interconnectivity of these two processes and emotional flexibility more broadly.

1.6.1 Specific studies, aims, and hypotheses

STUDY 1: Emotion-related brain activity to conflicting socio-emotional cues in unmedicated depression

Abnormalities in amygdala function have been implicated in major depression. However, results are inconsistent, and little is known about how the depressed brain encodes conflicting social signals. We sought to determine how the task relevance of socio-emotional cues impacts neural encoding of emotions in depression. Thus, we tested the prediction that MDD would be associated with increased amygdala activity in response to negative, yet reduced amygdala activity for positive, socio-emotional cues regardless of task-relevance (i.e., whether the emotional facial expressions were presented centrally or peripherally in the visual field). This prediction is based on the negative information processing biases observed in MDD.

STUDY 2: The neural correlates of regulating positive and negative emotions in medication-free major depression

This study adapted emotion regulation techniques to reflect elements of cognitive behavioural therapy (CBT) and related psychotherapies to delineate neurocognitive abnormalities associated with modulating the negative cognitive style in MDD. We predicted that MDD would be associated with abnormal activation of dorsal and lateral regions of the prefrontal cortex during both negative and positive emotion regulation. More specifically, we predicted that we would observe reduced activity in the dlPFC, vlPFC, and vmPFC of MDD patients, as well as reduced regulation efficacy as measured by subject reporting. This prediction is based on emotion regulation studies in healthy participants and individuals with MDD, as well as those studies that have examined brain changes associated with CBT treatment.

STUDY 3: The pattern of structural connectivity of the amygdala to a network of brain regions predicts individual differences in anxiety.

In this experiment we combined diffusion-weighted imaging, a measure of structural connectivity in the brain, with multiple regression to determine individual differences in trait-anxiety. Importantly, this approach allowed for the identification of multiple brain regions that are connected, either directly or indirectly, to the amygdala. Furthermore, we were able to determine how the robustness of these multiple connectivity pathways contributes to individual differences in trait-anxiety. We predicted that while greater amygdala connectivity with brain regions implicated in extinction learning (vmPFC) would relate to low trait-anxiety, high-trait anxiety would be associated with greater connectivity to regions involved in perception (visual regions of occipital cortex). This prediction comes from the few studies of DWI imaging studies that investigated individual differences in anxiety and studies of functional connectivity (correlating BOLD activity between these regions).

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CHAPTER 2

2 Emotion-related brain activity to conflicting socio-emotional cues in unmedicated depression¹

Abstract

Background: Abnormalities in amygdala function have been implicated in major depression. However, results are inconsistent, and little is known about how the depressed brain encodes conflicting social signals. We sought to determine how the task relevance of socio-emotional cues impacts neural encoding of emotion in depression.

Methods: Eighteen medication-free depressed patients and 18 matched controls participated in an fMRI experiment. Whole-brain analyses and a region-of-interest approach was used to measure amygdala activity during the presentation of fearful, happy, or neutral target faces with congruent, incongruent, or neutral distracters.

Results: Greater amygdala activity to target fearful faces was associated with depression, as was attenuated amygdala activity to target and peripheral happy faces. Although no group differences emerged in the amygdala to unattended fearful faces, we observed reduced ventrolateral and dorsomedial prefrontal activity in depressed individuals during this condition.

Limitations: Nine patients had a history of anti-depressant use, though they were unmedicated for at least three months at testing.

Conclusions: Depression was associated with reduced amygdala reactivity to positive social stimuli. However, enhanced amygdala responsiveness to negative emotional cues was only observed to target (attended) expressions. The results highlight the need to further determine factors that affect emotional reactivity in depression.

¹ Chapter 2 is published as: Greening, SG, Osuch, E, Williamson, PC, Mitchell, DGV (Accepted) Emotion-related brain activity to conflicting socio-emotional cues in unmedicated depression. Journal of Affective Disorders.

2.1 Introduction

Depression is associated with a negative cognitive style that is thought to play a key role in initiating and maintaining depressed mood (Beck et al., 1979). However, depression is also often associated with compromised social and interpersonal functioning (Paykel, 2002, Schelde, 1998), which appears to be an important risk factor for the disorder (Kaplan et al., 1987). At a neural level, abnormal activation of emotion-related brain regions to salient socio-emotional stimuli is associated with depression (Surguladze et al., 2004, Dannlowski et al., 2007) and depression vulnerability (Elliott et al., 2012). The majority of studies that examine neural responding to social cues in major depression involve single, static, unambiguous facial expressions. Although social situations are dynamic, involving multiple players, and often discordant social cues, much less is known about how conflicting emotional cues are encoded in the depressed brain. It is particularly unclear how the task-relevance (i.e., central versus peripheral) of competing socio-emotional cues influences the neural regions involved in emotional responding.

There is considerable evidence implicating the amygdala in emotion, and emotional responses to social stimuli (Phelps and LeDoux, 2005). For example, negative mood-induction has been shown to correlate with amygdala sensitivity (Berna et al., 2010, Schmitz et al., 2009), and electrical stimulation of the amygdala induces positive and negative emotions (Lanteaume et al., 2007). The amygdala is metabolically hyperactive (Drevets et al., 1992) in depressed patients, a pattern which resolves following anti-depressant treatment (Drevets et al., 2002). In addition, enhanced amygdala activity to negative cues, when present, has been found to resolve with treatment (Fales et al., 2009, Sheline et al., 2001, Victor et al., 2010). Collectively, the evidence implicates enhanced amygdala activity with emotional reactivity and depression, and supports using activity in this structure as a physiological index of emotional encoding and responsiveness.

Here we used fMRI to examine how the brain integrates conflicting basic socio-emotional signals in unmedicated depressed patients and matched controls. The study was designed to address the question of how incongruent (happy, fearful and neutral)

facial expressions are integrated with task-relevant social cues at a neural level in patients with depression. Specifically, the current study sought to determine whether target versus peripheral socio-emotional cues have a differential impact on neural activity in the amygdala and other emotion-related structures. While others have demonstrated that heterogeneity between groups can influence neural responding to facial expressions (Fournier et al., 2012), the present study is the first to assess whether task demands (i.e., socio-emotional context) influence the within-subject variability of amygdala reactivity observed in other studies. Thus, we tested the prediction that, consistent with a negative information processing bias, depression would be associated with enhanced amygdala activity for negative, and reduced amygdala activity for positive socio-emotional cues irrespective of task-relevance (regardless of whether they were presented centrally or peripherally). On the basis of studies suggesting that the amygdala is modulated by task demands (Mitchell et al., 2007, Pessoa et al., 2002), an alternative prediction is that amygdala reactivity would vary as a function of whether or not the socio-emotional cues were task-relevant.

2.2 Methods

2.2.1 Participants

Eighteen medication-free outpatients with a primary diagnosis of major depressive disorder (MDD) were recruited for study participation from London Health Sciences Centres and via community advertisements in London, Ontario (Mean age=26.61, SD=11.7, range=16-59; 12 female, 6 male). Nine patients were anti-depressant naïve at the time of scan, and the remainder were medication-free for at least three months ($M_{\text{months}}=30.8$, range =3 to 60 months); all were experiencing a major depressive episode at the time of scanning, as determined by trained individuals using the Structured Clinical Interview for the DSM-IV-TR (First et al., 2002). Patients with a history of head injury, neurologic illness, or depression resulting from a general medical condition or substance abuse were excluded. Patients with a comorbid diagnosis other than anxiety or past alcohol abuse were also excluded; and all reached diagnostic criterion for MDD, which was not

attributed to any other comorbid diagnosis. While six patients were experiencing their first major depressive episode at the time of the scan, the remainder were experiencing at least their second major depressive episode. Six patients had comorbid anxiety disorders: two with social anxiety disorder (SAD) without agoraphobia, three with post-traumatic stress disorder (PTSD), one with PTSD and SAD without agoraphobia; and two had a history of alcohol abuse (not within a month of testing). We performed independent t-tests contrasting depressed patients with and without comorbid anxiety revealing no significant differences between the two subgroups of patients ($p > 0.25$ for all), and confirming their inclusion did not significantly bias the results presented. Patients who reported claustrophobia, or who had any contraindications for MRI were not enrolled. A control group (CTL) of eighteen healthy volunteers matched for age, sex and handedness were recruited from the community. CTLs had no history of psychiatric illness as determined by the SCID, and reported having no first-degree relative with a known DSM-IV Axis-I or Axis-II disorder ($M_{age}=27.89$, $SD=11.26$, range =18-54; 12 female, 6 male). There was no significant group difference in age, [$t(34)=0.333$; $p>0.7$], or IQ based on the Wechsler Abbreviated Scale of Intelligence [WASI; $t(31)=1.07$, $p>0.3$; WASI scores were missing from 3 participants (2 in the MDD group) due to attrition]. Prior to scanning, participants completed the Beck Depression Inventory (BDI; Beck et al., 1996). Participants with MDD had significantly higher scores than controls [$BDI_{mean}(SD)$: MDD=24.56(9.8), CTL=1.6(2.4); $t(36)=9.64$, $p<0.001$]; the mean BDI score was indicative of moderate depression (severity ranging from mild to severe). All subjects granted informed written consent, and the study was approved by the Health Science Research Ethics Board at the University of Western Ontario, Canada.

2.2.2 Mixed Emotions Task

To test the impact of task-relevant and task-irrelevant emotional cues on the neural response of individuals with depression, participants completed a variant of the “mixed emotions task” (Amting et al., 2009; Figure 2.1). Participants viewed greyscale stimuli consisting of a central facial expression surrounded by four distracter faces. Throughout the experiment, participants were instructed to maintain fixation on cross-

faces located at the centre of the screen, and judge the emotion of the central (target) facial expression while ignoring the peripheral distracter faces. Participants entered their responses “as quickly and as accurately as possible” via button presses. The target-response pairings were counter-balanced across participants. There were 36 trials for each of the nine conditions, for a total of 324 trials divided equally between six “runs” of the task. The run order was counter-balanced across subjects.

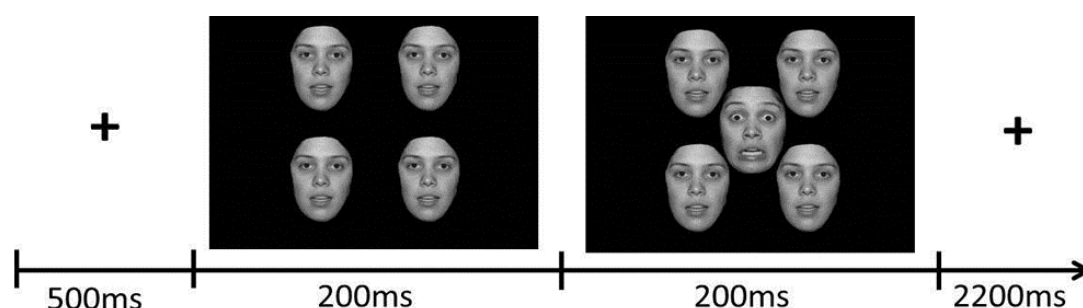


Figure 2.1 Mixed emotion task required participants to fixate on the centre of the screen, and report the facial expression of the central face

The task conformed to a randomized rapid event-related design, with each trial consisting of: a fixation cross, the distracter array of 4 faces presented alone, the target face presented centrally along with the distracter array, and an inter-trial interval with fixation. Six jitter trials of 3.25 seconds and six of 3.5 seconds randomly occurred throughout each of the six runs, and served to add temporal variability and aid in the individual subject regression analyses. The target-distracter stimulus pairings consisted of all permutations of fearful, happy, or neutral facial expressions, which resulted in 9 distinct conditions. In all, expressions from 18 (9 male, 9 female) individual actors were used, which varied between each array. Within stimulus arrays, faces of the same actor were used for both the target and distracter. Participants were instructed to ignore the distracter faces and respond as quickly and accurately as possible via a button press with the index, middle, or ring finger.

2.2.3 FMRI data acquisition

Participants were scanned at the Centre for Metabolic Mapping, in the Robarts Research Institute's 3T Siemens scanner equipped with a 32-channel head coil. BOLD changes were measured using a T2*-gradient echo-planar sequence (time to repetition = 3000ms, time to echo = 30ms; 120x120mm matrix; field of view = 24cm). Seventy-nine volumes were collected per run, and complete brain coverage was obtained with 45 interleaved slices of 2mm by 2mm in plane and a slice thickness of 2.5mm (forming voxels of 2x2x2.5 mm). The session ended with a high resolution T1 weighted whole-brain anatomical scan (time to repetition = 2300ms, time to echo = 4.25ms; Field of View = 25.6cm; 192 axial slices; voxel dimensions = 1mm isovoxels; 256X256mm matrix).

2.2.4 FMRI analysis

Individual and group analyses were conducted using Analysis of Functional NeuroImages software (Cox, 1996) following procedures adopted in our previous work (Greening et al., In Press). In brief, following motion correction, the functional data were aligned to the anatomical data and both were transformed into the standard space of Talairach and Tournoux. The dataset for each subject was spatially smoothed (4 mm isotropic Gaussian kernel) and scaled to percent signal change from the mean voxel activity. Regressors were produced by convolving the train of stimuli for each condition (from distracter onset to target-with-distracter offset) with the gamma-variate hemodynamic response function. General linear model regression was performed with a regressor for each of the nine conditions (error trials were modelled separately as regressors of no-interest). Baseline plus linear drift and quadratic trend were also modelled. This produced beta coefficients and t-values for each of our experimental conditions at each voxel, which were then used in the group analyses.

To test our primary hypotheses concerning the impact of attended and unattended emotional cues on the neural response, we compared 4 critical experimental conditions

across groups. These conditions were: a fearful target with neutral distracters (FN), a happy target with neutral distracters (HN), a neutral target with fearful distracters (NF), and a neutral target with happy distracters (NH). This between-group analysis was performed using the mixed effects meta-analysis function in the AFNI software package (Chen et al., 2012). As the amygdala was our primary region-of-interest (ROI), we used a small volume correction (SVC) to identify clusters of significant activity within the anatomically defined right and left amygdala consistent with previous studies of emotional reactivity and depression (Fales et al., 2008, Victor et al., 2010). For the ROI analysis, clusters within the amygdala were identified that survived a family-wise error (FWE) correction to $p < 0.05$, requiring $k=5$ contiguous voxels to be significant at $p < 0.01$, two-tailed. An exploratory whole-brain analysis was also performed, which identified significant clusters that survived an FWE correction to $p < 0.05$ ($k > 30$ contiguous voxel; $p < 0.005$, two-tailed).

2.3 Results

2.3.1 Behavioural Results

Behavioural performance was analyzed with a 2 (Group: MDD, CTL) by 3 (Target: Fear, Happy, Neutral) by 3 (Distracter: Fear, Happy, Neutral) repeated measures ANOVA for both reaction time (RT; for correct responses) and accuracy data (proportion of target emotions correctly categorized; see Table 2.1 for details). The RT analysis revealed a main effect of target [$F(2,34)=44.34$; $p < 0.001$]. RTs were significantly faster to happy relative to both fearful [$F(1,34)=64.6$; $p < 0.001$] and neutral targets [$F(1,34)=42.1$; $p < 0.001$], and to neutral relative to fearful targets [$F(1,34)=5.6$; $p < 0.05$]. No other effects were significant.

The analysis of accuracy revealed a main effect of target [$F(2,68)=19.5$; $p < 0.001$]. Participants responded more accurately to happy targets relative to both fearful [$F(1,34)=23.9$; $p < 0.001$] and neutral targets [$F(1,34)=7.3$; $p < 0.05$]. In addition, participants responded more accurately to neutral relative to fearful targets [$F(1,34)=18.7$; $p < 0.001$]. No other effects were significant.

Table 2.1 Behavioural data reveals main effect of target facial expression irrespective of group and distracter expression

Condition	Reaction Time				Accuracy			
	MDD		CTL		MDD		CTL	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
FF	845.68	121.10	786.33	158.27	0.93	6	0.90	0.10
FH	857.12	141.97	803.25	160.08	0.92	7	0.91	0.08
FN	844.72	140.91	798.48	156.91	0.91	8	0.91	0.11
HF	727.55	113.54	690.42	120.61	0.98	2	0.97	0.04
HH	719.40	115.86	670.52	110.52	0.98	2	0.96	0.07
HN	733.95	128.32	683.49	107.04	0.97	3	0.96	0.06
NF	823.38	147.91	785.68	185.64	0.95	4	0.95	0.07
NH	826.59	150.68	770.86	165.95	0.96	4	0.94	0.07
NN	813.73	148.30	772.21	164.68	0.95	5	0.95	0.06

Mean (M) and standard deviations (SD) for reaction time (displayed in milliseconds) and accuracy (displayed in proportion correct) are shown for each group. There was a significant main effect of emotion for both reaction time and accuracy measures. Participants responded faster and more accurately on trials with happy targets relative to either fearful or neutral target conditions, and were significantly slower and less accurate on trials with fearful targets relative to trials with neutral or happy targets. With regard to reaction times, there was no significant main effect of distracter emotion [$F(2,68)=1.20$; $p=0.89$] or group [$F(1,34)=1.19$; $p=0.28$], nor were there any significant interactions [target emotion by group: $F(2,68)=0.06$, $p=0.94$; distracter emotion by group: $F(2,68)=0.43$, $p=0.65$; target by distracter emotion: $F(4,136)=1.88$, $p=0.12$; three-way interaction: $F(4,136)=0.423$, $p=0.79$]. With regard to accuracy, there was no main effect of distracter emotion [$F(2,68)=0.46$; $p=0.27$] or group [$F(1,34)=0.48$; $p=0.49$], nor were there any significant interactions [target emotion by group: $F(2,68)=0.05$, $p=0.95$; distracter emotion by group: $F(2,68)=1.34$, $p=0.27$; target by distracter emotion: $F(4,136)=0.23$, $p=0.92$; three-way interaction: $F(4,136)=0.96$, $p=0.43$]. [Abbreviations: FF = Fearful target with fearful distracters; FH = fearful target with happy distracters; FN = fearful target with neutral distracters; HF = happy target with fearful distracters; HH = happy target

with happy distracters; HN = happy target with neutral distracters; NF = neutral target with fearful distracters; NH = neutral target with happy distracters; NN = neutral target with neutral distracters.]

2.3.2 FMRI Results

To evaluate the neural encoding of task-relevant negative cues in MDD, we first contrasted conditions with emotional targets and neutral distracters across the MDD and control groups. In response to task-relevant negative emotional cues (FN condition), patients with MDD displayed significantly greater right amygdala activity relative to controls (Figure 2.2, left; threshold of $p < 0.01$, SVC to $p < 0.05$). Conversely, when the task-relevant emotional cue was positive (HN condition), the MDD group displayed significantly less right amygdala activity than CTLs (Figure 2.2, middle; threshold of $p < 0.01$, SVC to $p < 0.05$). The whole-brain analyses revealed no significant group differences during the presentation of either positive or negative task-relevant emotional cues.

To examine the encoding of non-target emotional stimuli in the presence of neutral social cues, we contrasted conditions with neutral targets and emotional distracters across the two groups. When negative distracters were present with a neutral target, there were no significant differences between the two groups within the amygdala. However, when positive distracters were present with a neutral target, we observed significantly reduced activity in the left amygdala (extending into anterior parahippocampal gyrus) of the MDD group relative to the CTLs (Figure 2.2, right; threshold of $p < 0.01$, SVC to $p < 0.05$).

The whole-brain analysis revealed that there were significant group differences when negative distracters were present with a neutral target (see Table 2.2). Specifically, we observed that the MDD group had reduced activity relative to CTLs in regions implicated in the executive control of emotion (Mitchell, 2011, Ochsner and Gross, 2005), including dmPFC and left vIPFC (Figure 2, threshold of $p < 0.005$, whole-brain

FWE corrected to $p < 0.05$). The whole-brain analysis for task-irrelevant positive cues with a neutral target revealed no significant differences between groups.

Two exploratory analyses comparing the conditions with competing facial expressions (FH and HF) independently across groups revealed no significant group differences in either the amygdala, or whole-brain. In none of the analyses was BOLD activity significantly correlated with depression severity.

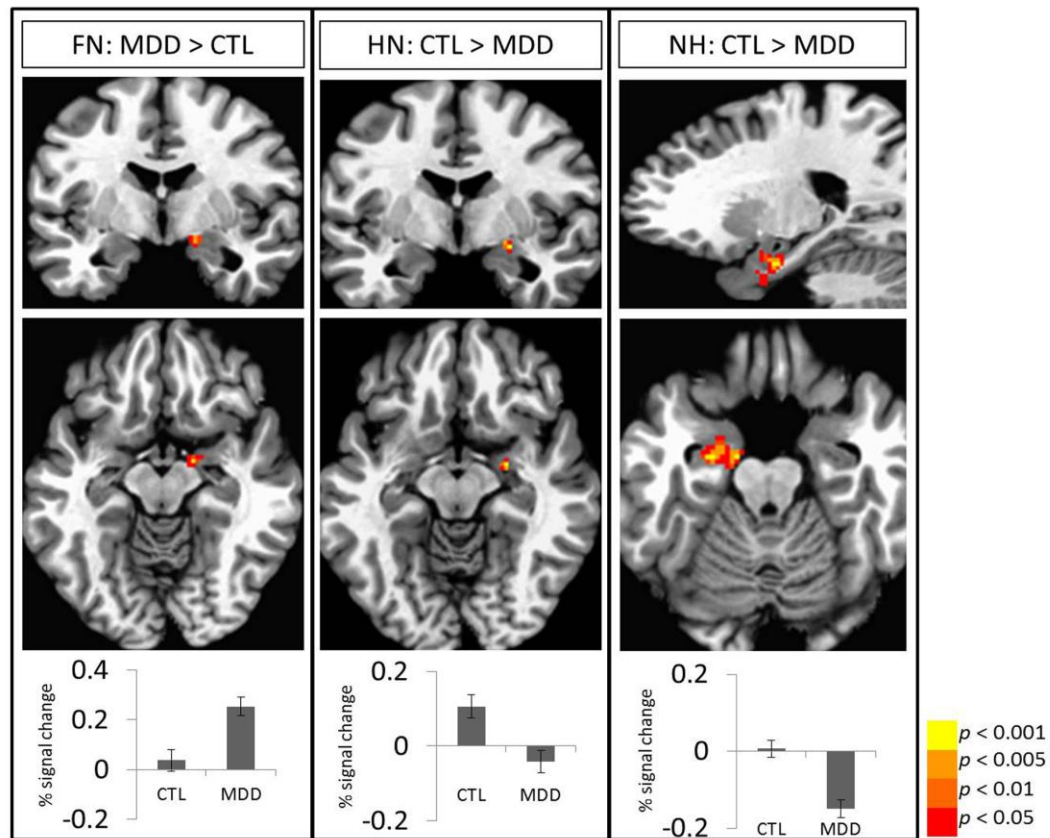


Figure 2.2 BOLD response in the amygdala using a region of interest approach displays evidence for the preferential processing of central but not peripheral negative emotional faces

Left – Greater activity in the right amygdala (t -value = 3.01; Centre of Mass: $x = 16$, $y = -6$, $z = -11$) during the fearful target with neutral distracter condition for patients with MDD relative to controls [$M_{\% \text{signal change}}(\text{SE})$: MDD = 0.253(0.037); CTL = 0.037(0.043)]. **Middle** – Attenuated right amygdala activity (t -value =

3.23; Centre of Mass: $x = 22, y = -7, z = -9$) during the happy target neutral distracter condition for patients with MDD relative to controls [$M_{\% \text{signal change}}(\text{SE})$: MDD = $-0.042(0.030)$; CTL = $0.106(0.031)$]. **Right** – Attenuated activity in a region including the amygdala and parahippocampal gyrus ($t\text{-value} = 3.41$; Centre of Mass: $x = -2, y = -9, z = -23$) during the neutral target with happy distracter condition for MDD relative to controls [$M_{\% \text{signal change}}(\text{SE})$: MDD = $-0.147(0.023)$; CTL = $0.008(0.022)$]. ROI-based correction analysis was performed at a two-tailed threshold of $p < 0.01$, corrected to a family wise error rate of $p < 0.05$. In order to depict the full extent of activation, all contiguous voxels that reached an uncorrected p -value ranging from 0.001 to 0.05 are displayed. Active clusters are displayed on the T1-weighted Talairach-Tournoux template (TT_N27) in AFNI.

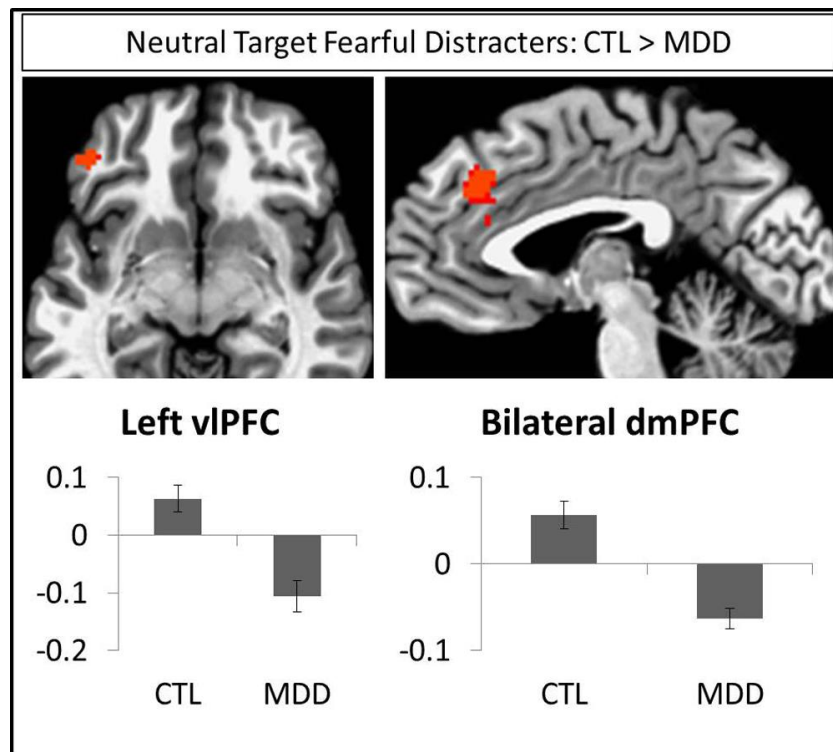


Figure 2.3 Whole-brain analysis reveals greater recruitment of cognitive control regions of the cortex in controls when distracting fearful faces are present

Reduced activity was observed in left ventrolateral prefrontal cortex and dorsomedial prefrontal cortex bilaterally in MDD relative to control participants during the neutral target with fearful distracter condition. The whole-brain analysis was conducted at a two-tailed threshold of $p < 0.005$, and corrected to a family wise error rate of $p < 0.05$. Clusters are presented at the whole-brain threshold of $p < 0.005$. Active clusters are displayed on the T1-weighted Talairach-Tournoux template (TT_N27) in AFNI.

Table 2.2 Regions surviving exploratory whole-brain analysis during fearful task-irrelevant distracters (NF)

Location	R/L	BA	X,Y,Z	Cluster Size	T-value	MDD %Sig.Change	CTL %Sig.Change
<i>CTL > MDD during Neutral Target with Fearful Distracters condition</i>							
Dorsomedial PFC	R/L	9/32/6	-3,32,37	196	3.80	-0.063(0.011)	0.057(0.018)
Ventrolateral PFC	L	47	-43,38,-5	57	3.70	-0.106(0.027)	0.063(0.023)
Superior Frontal Gyrus	R	8/9	9,54,46	33	3.49	-0.028(0.024)	0.168(0.042)
Supplementary Motor Cortex	R	6	15,5,69	47	3.46	-0.070(0.028)	0.071(0.024)
Supramarginal Gyrus	R	40	63,-47,28	49	3.42	-0.071(0.025)	0.115(0.034)
Supramarginal Gyrus	L	40	-63,-47,29	34	3.45	-0.071(0.025)	0.115(0.034)

All clusters were thresholded at $p < 0.005$, corrected to $p < 0.05$ (FWE, $k > 30$). The Brodmann location (BA) is provided, along with coordinates for the centre of mass in MNI space (X,Y,Z). Cluster size represents the number of contiguous voxels sharing a face, and the T-value is the mean T-value for all voxels in the cluster. The final two columns present the mean (standard deviation) percent signal change per group in each cluster.

2.4 Discussion

The present study examined how the brain integrates conflicting basic socio-emotional signals in unmedicated depressed patients and matched controls. We observed exaggerated amygdala activity to negative stimuli in participants with MDD only when

negative stimuli were task-relevant. Consistent with the idea that negative reactivity in depression is modulated by task relevance, amygdala activity associated with peripheral negative expressions was not significantly different from controls. However, amygdala activity was significantly reduced in patients with MDD relative to controls in the presence of positive stimuli (happy faces) regardless of task relevance. Lastly, the presence of task-irrelevant negative expressions was associated with greater activity in controls relative to depressed participants in neural regions implicated in emotion regulation (dmPFC and vLPFC).

2.4.1 Relationship to previous studies

The empirical picture concerning emotional reactivity and the amygdala in depression is complex. Previous studies examining amygdala reactivity to facial emotions in depression have found hypo-activity (Lawrence et al., 2004, Ritchey et al., 2011), hyper-activity (Victor et al., 2010, Suslow et al., 2010), and no significant differences (Almeida et al., 2010) relative to controls. This inconsistency may at least in part be accounted for by the heterogeneous nature of major depression (Fournier et al., 2012). The present study provides evidence that, even within a sample of patients with MDD, abnormal emotion-related activity can vary as a function of task demands. One possibility is that some of the disparate findings observed in the literature may in part be due to how task demands influence negative stimulus encoding, and the extent to which stimuli map onto depressive schema (e.g., sad faces may be more readily integrated than fearful ones, Neumeister et al., 2006). However, it is important to note that variability may exist between attentional manipulations (e.g., Fales et al., 2008). These results highlight the need for future work in further defining the parameters influencing amygdala reactivity in depression.

2.4.2 Emotion control and prefrontal cortex

It is noteworthy that relative to the control group, depressed patients showed significantly reduced dmPFC and vlPFC activity in response to trials involving negative distracters. Both areas have been implicated in regulating or representing the influence of emotional distracters on brain and behaviour (Ochsner and Gross, 2005, Mitchell, 2011). It is tempting to speculate that the observed abnormalities may be contributing to dysregulated mood in depression. However, interpreting this effect in the current study may be complicated by the absence of a significant group by distracter interaction at the behavioural level. Nevertheless, even without such behavioural effects, the BOLD response has provided a sensitive metric of stimulus encoding at a neural level in healthy (e.g., Mitchell et al., 2007, Pessoa et al., 2002) and depressed (e.g., Elliott et al., 2002, Suslow et al., 2010) groups. Indeed, lack of group differences can be advantageous, as the results are less susceptible to confounds related to time-on-task differences or sampling error (Elliott et al., 2002, Knutson et al., 2008). Interestingly, depression has been associated with functional abnormalities in both dmPFC and vlPFC (Johnstone et al., 2007, Mitterschiffthaler et al., 2008). Further research is required to determine whether depression is related predominantly to dysfunction in “bottom-up” emotion-related areas, or is combined with abnormalities in “top-down” cortical regions associated with emotion regulation.

2.4.3 Implications for Neurocognitive Models of Depression

Depression has long been associated with a negative-bias that prioritizes negative information processing (Beck, 2008). One of the mechanisms by which abnormalities in amygdala responsiveness is thought to influence negative information processing is by enhancing the salience of sensory representations of either internal or external emotional information (Amting et al., 2010, Vuilleumier, 2005). At a neural level, the amygdala in depressed individuals may augment endogenous depressive representations (and associated stimuli) at the expense of dissimilar ones. In support, enhanced amygdala activity has been observed in studies involving task-relevant facial expressions (Fu et al.,

2004, Surguladze et al., 2005). However, our results suggest that the extent to which negative external stimuli elicit pathological neural processes is influenced by their relevance to the current task. Thus, depression was associated with enhanced amygdala activity to target fearful faces, but not peripheral fearful faces. For positive stimuli, however, depression was associated with significantly reduced amygdala activity relative to controls regardless of whether the stimuli were task-relevant. These latter findings appear partially consistent with an alternate theory of depressive cognitive style, emotion context insensitivity (ECI). ECI posits that MDD is associated with attenuated emotional reactivity to both positive and negative cues (Rottenberg et al., 2005). Indeed, individuals with depression have displayed reduced amygdala activity (Drevets, 2001, Thomas et al., 2001) in response to negative facial expressions, and reduced mPFC activity to emotional displays of social groups (Elliott et al., 2012). Our results together with prior studies illustrate the complexity of emotional processing in depression, and suggest that future work is required to further delineate the parameters that influence emotional reactivity in the disorder.

2.4.4 Limitations

Our depressed sample combined individuals who were medication naïve with those who had previously taken anti-depressants. Given that anti-depressants have been shown to cause neurological changes (Bessa et al., 2009), future research involving medication naïve patients combined with longitudinal assessments following treatment would offer further insight into depression. Additionally, the present study used fearful expressions as negative stimuli, and differential effects might be observed with the inclusion of other emotions, particularly sadness (Victor et al., 2010), which might map onto existing depressive representations.

2.4.5 Conclusion

The findings of the current study suggest that while a negative processing bias was evident at a neural level when sufficient attention was directed to socio-emotional cues, reactivity to unattended emotional cues in depressed patients relative to controls may be either blunted (for positive distracters) or at similar levels (for negative distracters). One possibility is that preoccupation with idiosyncratic endogenous negative schemas in depression may reduce the capacity to integrate external cues, particularly discordant cues, or those that are not relevant to the current task. This work reconciles some of the apparent contradictions in the literature by suggesting that the extent to which a negative-encoding bias manifests depends on task-demands, and highlights the fact that heterogeneity may exist in emotional encoding even within a sample of depressed patients.

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CHAPTER 3

3 The neural correlates of regulating positive and negative emotions in medication-free major depression²

Abstract

Depressive cognitive schemas play an important role in the emergence and persistence of major depressive disorder (MDD). The current study adapted emotion regulation techniques to reflect elements of cognitive behavioural therapy (CBT) and related psychotherapies to delineate neurocognitive abnormalities associated with modulating the negative cognitive style in MDD. Nineteen non-medicated patients with MDD and 19 matched controls reduced negative or enhanced positive feelings elicited by emotional scenes while undergoing functional magnetic resonance imaging. Although both groups showed significant emotion regulation success as measured by subjective ratings of affect, the controls were significantly better at modulating both negative and positive emotion. Both groups recruited regions of dorsolateral prefrontal cortex (dlPFC) and ventrolateral prefrontal cortex (vlPFC) when regulating negative emotions. Only in controls was this accompanied by reduced activity in sensory cortices and amygdala. Similarly, both groups showed enhanced activity in vlPFC and ventral striatum when enhancing positive affect; however, only in controls was ventral striatum activity correlated with regulation efficacy. The results suggest that depression is associated with both a reduced capacity to achieve relief from negative affect despite recruitment of ventral and dorsal prefrontal cortical regions implicated in emotion regulation, coupled with a disconnect between activity in reward-related regions and subjective positive affect.

² Chapter 3 is published as: Greening, SG, Osuch, E, Williamson, PC, Mitchell, DGV (In Press) The neural correlates of regulating positive and negative emotions in medication-free major depression. *Social, Cognitive and Affective Neuroscience*.

3.1 Introduction

Major depressive disorder (MDD) is among the most prevalent, costly, and debilitating psychiatric disorders (World Health Organization, 2003). A ‘negative cognitive triad’ is thought to play a key role in the initiation and maintenance of depressed mood, consisting of a persistent negative idiosyncratic appraisal of the self, the future, and the world (Beck et al., 1979). It has also been argued that one of the key abnormalities behind depressive illnesses is dysfunction in neural systems supporting adaptive emotion regulation (Davidson et al., 2002). The goal of a number of psychotherapies therefore is to target negative-biases, and to increase the efficacy of emotion regulation. Consequently, elucidating the role of neural regions involved in resolving negative-biases and fostering adaptive emotional responding in depression is vitally important for improving the efficiency, efficacy, and durability of the therapeutic response (Clark and Beck, 2010, Linden, 2006).

The effortful regulation of emotion is thought to involve dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC), and dorsomedial prefrontal cortex (dmPFC), which modulate, either directly or indirectly, emotion encoding in regions such as the amygdala and ventral striatum (Ochsner et al., 2002, Ochsner et al., 2004, Wager et al., 2008, Urry et al., 2006, Han et al., 2011). However, the efficacy associated with emotion regulation varies depending on the strategy adopted as indicated by neural, physiological, and behavioural markers of affect (e.g., Kross et al., 2009, Gross, 1998, Goldin et al., 2008). For example, some strategies may even exacerbate emotional dysfunction (Gross, 1998, Campbell-Sills and Barlow, 2007). Consideration of the specific regulation strategy adopted is therefore critical when interpreting the clinical significance of results from emotion regulation studies.

Considerable research has demonstrated the importance of the ventromedial prefrontal cortex, including the subgenual region (Mayberg et al., 2005), in the etiology of depression (Drevets et al., 1992, Koenigs et al., 2008). Notably, much of this evidence comes from studies using positron emission tomography (PET), which is often more robust than fMRI to the signal loss caused by susceptibility-artifact (Devlin et al., 2000, Veltman et al., 2000). However, it is also important to note the evidence that lateral

prefrontal regions involved in emotion regulation have also been implicated in current models of MDD (Phillips et al., 2003, Price and Drevets, 2010). Past research has demonstrated that MDD is associated with reduced resting metabolism in dlPFC (Mayberg, 2002) and hyper-metabolism in vlPFC (Drevets et al., 1992). In addition, histological evidence from post-mortem studies indicates that neuronal and glial density within the dlPFC and vlPFC of depressed patients is reduced (Rajkowska et al., 2001, Rajkowska et al., 1999). While some suggest that recovery from MDD following medication is related to enhanced activity in dlPFC (Fales et al., 2009, Kennedy et al., 2001), others have found that successful treatment with CBT was associated with reduced activity within dlPFC and vlPFC (Goldapple et al., 2004, Ritchey et al., 2011). When healthy, these regions are thought to modulate stimulus encoding in a manner that ultimately influences activity in emotion-related brain regions including the amygdala and ventral stratum, which have both been implicated in the pathophysiology of depression (Phillips et al., 2003, Drevets et al., 1992). One way to better understand the role of dlPFC and vlPFC in emotion regulation and CBT is to examine these two processes in the context of active emotion regulation.

To date, strategies used in emotion regulation studies of depression have differed from those adopted in typical cognitive-based therapies. For example, patients have been asked to take the perspective of a detached observer (Beauregard et al., 2006, Erk et al., 2010), or imagine that the situation is fake or unreal (Johnstone et al., 2007, Heller et al., 2009, Light et al., 2011). This is crucial because various forms of regulation differentially recruit regions of the prefrontal cortex (Goldin et al., 2008, Ochsner et al., 2004, Kross et al., 2009). Furthermore, only one study to date (Heller et al., 2009) has examined patients' capacity to explicitly up-regulate positive affect. This knowledge gap is particularly critical given that reduced behavioural responsiveness to positive emotions predicts poorer prognosis (Rottenberg et al., 2002), and a number of studies have found that amygdala reactivity to positive but not negative cues is correlated with depression severity (Suslow et al., 2010, Victor et al., 2010). Thus, collectively, the evidence suggests that distinct emotion regulation strategies can have different effects at a behavioural and physiological level, and emotional reactivity to positive stimuli predicts therapeutic response. Consequently, further research using emotion regulation techniques

that mirror strategies employed in cognitive therapies and target positive as well as negative affect is essential.

Here we used functional magnetic resonance imaging (fMRI) in conjunction with an emotion regulation task we adapted to incorporate elements of CBT and cognitive-based therapies. Patients with MDD and matched controls attempted to reduce their emotional response to sad stimuli and enhance their response to positive ones. We tested the hypothesis that depression would be associated with abnormal recruitment of prefrontal regions implicated in emotion regulation. Specifically, we predicted that patients with depression would show reduced regulation efficacy, coupled with functional abnormalities in dlPFC and vlPFC. In addition, we predicted that this would be accompanied by dysfunctional modulation of amygdala and ventral striatum by negative and positive regulation trials, respectively.

3.2 Methods

3.2.1 Participants

Nineteen medication-free outpatients with a primary diagnosis of MDD were recruited for study participation from London Health Sciences Centres and via community advertisements in London, Ontario ($M_{age}=26.79$, $SD=11.4$, range=16-59; 13 female, 6 male). Ten patients were anti-depressant naïve at the time of scan, and the remainder were medication-free for at least three months ($M_{months}=30.8$, range =3 to 60 months). All participants were experiencing a major depressive episode at the time of scanning, as determined by a clinical research assistant or the primary investigator using the Structured Clinical Interview for the DSM-IV-TR (SCID; First et al., 2002), both of whom underwent the required training as per the SCID manual. Patients with a history of head injury, neurologic illness, or depression resulting from a general medical condition or substance as determined by the SCID, were excluded. Patients with a comorbid diagnosis other than anxiety or past alcohol abuse were also excluded. Seven participants were experiencing their first major depressive episode at the time of the scan, while the remainder were experiencing at least their second major depressive episode. All patients

reached diagnostic criteria for MDD, which was not attributed to any other comorbid diagnosis. Seven patients had comorbid anxiety disorders: two with social anxiety disorder (SAD) without agoraphobia, four with post-traumatic stress disorder (PTSD), one with PTSD and SAD without agoraphobia, and two had a history of alcohol abuse. One patient had last abused alcohol a year from the time of scan, and the other patient last abused one month from the time of scan. Notably, the between-group fMRI analyses described below were repeated after excluding patients with PTSD or patients with alcohol abuse. These additional analyses did not produce substantively different results, and so are not presented. Patients who presented as euthymic at the time of contact with the research program, who reported claustrophobia, or who had any contraindications for participation in the MRI scanner were not enrolled in the study. Additionally, data from one subject was excluded because treatment with anti-depressants was commenced between the date of the SCID interview and the scan session. A control group (CTL) of 19 healthy volunteers matched for age, sex and handedness were recruited from the community for the study. Participants in the control group had no history of psychiatric illness as determined by the SCID, and reported having no first-degree relative with a known DSM-IV axis-1 or axis-2 disorder (Mage=27.63, SD=11.0, range =18-54; 13 female, 6 male). There was no significant difference in age between groups [$t(36)=0.231$; $p>0.8$] nor were there significant differences in intelligence quotient (IQ) on the Wechsler Abbreviated Scale of Intelligence [WASI mean(SD): MDD=108.65(12.3), CTL=113.17(8.9); $t(33)=1.251$, $p>0.2$; WASI scores were missing from 3 participants (2 in the MDD group) due to attrition]. Immediately prior to scanning, participants completed the Beck Depression Inventory (BDI; Beck et al., 1996). As expected, participants with MDD had significantly higher BDI scores than controls [BDI mean(SD): MDD=25.53(10.4), CTL=1.6(2.3); $t(36)=9.768$, $p<0.001$]; the mean BDI score for the MDD group was indicative of moderate depression, though severity ranged from mild to severe. The mean estimated length of the current depressive episode at the time of scan based on subject report was 7.8 weeks (ranging from 2 to 54 weeks), though the median length was 4 weeks. All subjects granted informed written consent, and the study was approved by the Health Science Research Ethics Board at the University of Western Ontario, Canada.

3.2.2 Task Design

The emotion regulation task was designed to have participants actively engage in a strategy to alter the feelings elicited by sad (negative) and positive emotional scenes (for task details see Figure 3.1), similar to previous studies in healthy controls (Ochsner et al., 2002, Ochsner et al., 2004). However, the current method differed from previous studies in that the regulation techniques were developed to reflect a strategy, similar to those used in cognitive behavioural and other cognitive-based therapies (CBT), to address the cognitive triad of dysfunctional schematic thinking associated with MDD (Beck et al., 1979). This strategy targeted the tendency of depressed patients to have negative thoughts about the self (e.g., feelings of worthlessness), the world or environment (e.g., the world is unfair), and the future (e.g., the future is hopeless). In the enhance condition participants were instructed to: “Acknowledge that the scene is positive. Further, that it does affect you, things can and do get even better, and the scene does reflect the real world”. During the reduce condition, participants were instructed to: “Acknowledge that the scene is negative. However, it does not affect you, things do not stay this bad, and the scene does not reflect the whole world”. It was further emphasized that participants should, using internal dialogue, elaborate upon any aspect of the script using self-relevant examples they felt would be most effective. There were 20 trials in each of the four experimental conditions (i.e., attend positive, attend negative, reduce negative, enhance positive), for a total of 80 trials across four runs. Additionally, the trial order in each run was randomized, and the 4 runs were counterbalanced across subjects. In a separate session prior to being scanned, participants were trained to use the regulation strategies and underwent a practice session of the task.

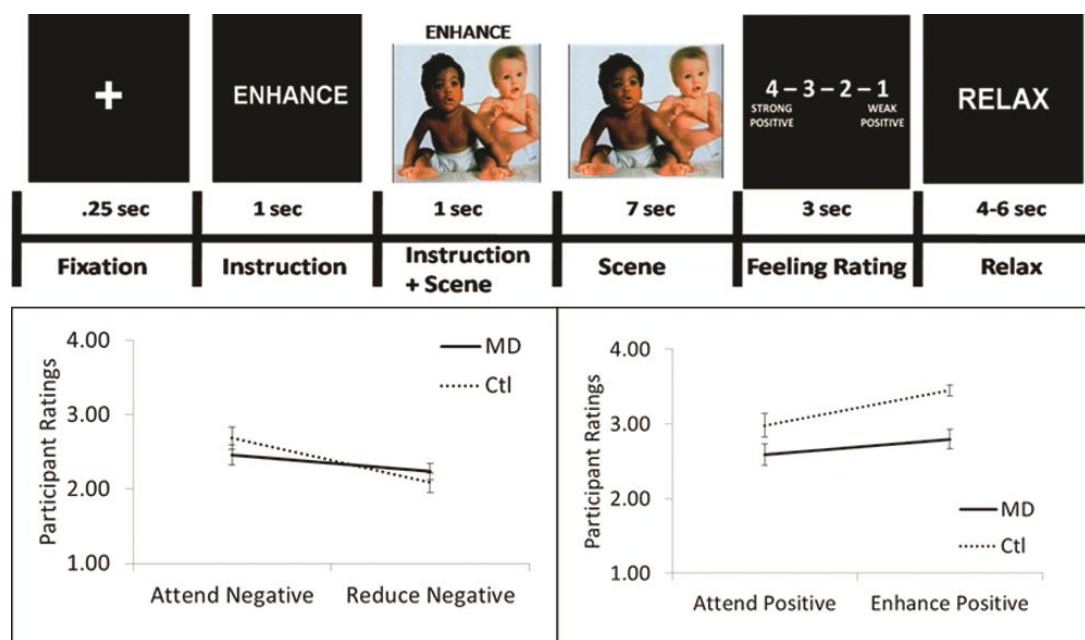


Figure 3.1 The emotion regulation task and behavioural results

Top – Sample of an enhance-positive trial. Each trial of the emotion regulation task was comprised of 5 events: 1) a fixation cross; 2) an instruction about the type of strategy to use while viewing the scene (i.e., attend positive or negative, reduce negative, or enhance positive); 3) a scene depicting either positive or negative emotional significance (i.e., a standardized image shown to elicit contentment/amusement or sadness); 4) a rating screen with a 4-point Likert scale during which participants rated the feelings evoked by the picture; 5) a screen with the word “relax”, during which time the participants could clear their minds before the next trial. The three instructional words of “attend”, “enhance”, and “reduce” each corresponded to an emotion regulation strategy that was taught to the participants prior to beginning the experiment. During the attend conditions, participants were instructed to identify the feeling associated with the scene and experience whatever feelings come naturally without changing them. **Bottom-Left** – Mean emotional rating for negative trials [y-axis: strength of emotional response (ranging from 1=weak to 4=strong)] reveals a main effect of instruction and a significant group X instruction interaction showing enhanced regulation efficacy in CTL relative to MDD group. Error bars depict standard error of the mean. **Bottom-right** – mean emotional rating for positive trials (y-axis: 1=weak positive to 4=strong positive emotional

response) reveals a main effect of group, a main effect of instruction, and a significant group by instruction interaction characterized by enhanced regulation efficacy in CTL relative to MDD group (p). Error bars depict standard error of the mean. All effects were significant at $p < 0.05$.

3.2.3 Stimuli

A total of 20 sad and 20 positive scenes were used in the task, each one appearing twice (never in the same run), once in an attend condition and once in a regulate condition, with the order counterbalanced across participants. The emotional scenes were taken from the International Affective Picture System (IAPS; Lang et al., 2008), and were not significantly different in terms of normative ratings of arousal ($M_{\text{positive}}(\text{SD}) = 5.03(0.55)$, $M_{\text{sad}}(\text{SD}) = 5.08(0.62)$; $p > 0.8$). In order to increase the relationship between the stimuli and the emotions central to depression, images were chosen on the basis of refined normative ratings developed by Mikels et al. (2005). These refined ratings allowed us to identify a subset of scenes that elicited one discrete emotion more than others. Specifically, our sad scenes were those that reliably elicit sadness, and the positive scenes were images that reliably elicit contentment/amusement (Mikels et al., 2005).

3.2.4 FMRI data acquisition

The experimental task was completed at the Centre for Metabolic Mapping, in the Robarts Research Institute's 3T Siemens scanner equipped with a 32 channel head coil. Participants completed six functional MRI runs during which blood-oxygenation-level-dependent (BOLD) changes were measured using a T2*-gradient echo-planar sequence (EPI; time to repetition = 3000ms, time to echo = 30ms; 120x120mm matrix; field of view = 24cm). Seventy-nine volumes were collected per run, resulting in run durations of 3.95 minutes. Complete brain coverage was obtained with 45 interleaved slices of 2mm by 2mm in plane and a slice thickness of 2.5mm (forming voxels of 2x2x2.5 mm). Our current parameters involved whole-brain coverage and were not specifically optimized

for signal detection in the ventral PFC. There was notable susceptibility-artifact in regions of the ventral PFC (see Figure 3.2), which may account for a lack of effects in these regions (Devlin et al., 2000, Veltman et al., 2000). The session ended with a high-resolution T1-weighted anatomical scan that covered the whole brain (time to repetition =2300ms, time to echo =4.25ms; Field of View=25.6cm; 192 axial slices; voxel dimensions =1mm isovoxels; 256 X 256mm matrix).

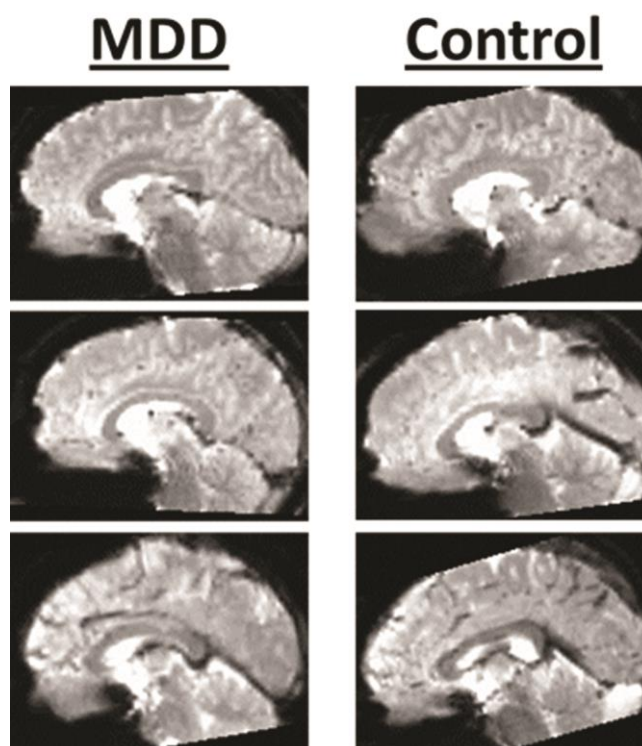


Figure 3.2 Raw EPI images showing slices through VMPFC of 6 representative participants

There was notable susceptibility-artifact in regions of the ventral PFC, which may account for a lack of effects in these regions. Left) Raw EPI images for three participants with MDD; Right) Raw EPI images for three control participants.

3.2.5 Behavioural analysis

Participants' mean emotional ratings were calculated for each of the four conditions from the trial-by-trial emotional rating screen (the 4-point Likert scale). The individual means were entered into two independent 2 (Group: CTL, MDD) X 2 (Condition: Regulation, Attend) ANOVAs (one for trials with sad scenes and the other for positive scene trials). We also computed both negative (sad trials) and positive (positive trials) regulation efficacy scores at the individual subject level. These scores reflected the mean absolute difference between emotional ratings during regulate-minus-attend trials. Thus, in the context of the current task a higher value for either negative or positive regulation efficacy was indicative of greater regulation success. This was used to examine correlations between regulation efficacy and ratings of depression severity (BDI), as well as regulation efficacy and functional activity.

3.2.6 fMRI analysis

Individual and group analyses were conducted using Analysis of Functional NeuroImages software (Cox, 1996). The first four volumes of each of the six runs were discarded to insure that magnetization equilibrium was reached. Motion correction was completed by registering all BOLD data in each run of the task to the first volume of the last experimental run. Next, the functional data were aligned to the anatomical data and both were transformed into the standard space of Talairach and Tournoux. The dataset for each subject was spatially smoothed with a 4 mm isotropic Gaussian kernel and the time series data of each voxel was scaled such that the coefficients produced by the regression analysis represented the percent signal change from the mean voxel activity. A first-level general linear model regression analysis was performed including a regressor for each of the 4 conditions of interest (attend positive, attend negative, enhance positive, reduce negative), which began at emotional scene onset and ended with emotional scene offset (a duration of 8 seconds). Regressors of no-interest were modelled for trials in which no response was detected, for the instruction epoch, and for the emotional rating and relax epochs. Participants were instructed to only respond during the rating epoch so as to

ensure that BOLD activity related to motor responses did not confound the events of interest. All Regressors were produced by convolving the train of stimuli with the gamma-variate hemodynamic response function. To account for voxel-wise correlated drifting, baseline plus linear drift and quadratic trend were also modelled. This produced beta coefficients and t-values for each of our experimental conditions at each voxel, which were then used in the group analyses described below.

In order to test our primary hypotheses concerning the neural correlates of emotion regulation in MDD, we performed analyses examining the effects of group (MDD versus CTL) on regulating positive and negative affect. This between-group analysis was performed using the mixed-effects multilevel analysis function in the AFNI software package (Chen et al., 2012). A two-sample mixed effects analysis was then possible for each of the experimental conditions. Whole-brain analysis of the BOLD data identified significant clusters that survived a family-wise error rate (FWE) correction to $p < 0.05$ ($k > 47$ contiguous voxel; $p < 0.005$ uncorrected threshold, two-tailed). For the amygdala, an a priori region of interest (ROI), we used a more liberal threshold of $p < 0.01$ (uncorrected, $k \geq 10$ contiguous voxels) consistent with thresholds adopted in previous studies of emotion in depression (Victor et al., 2010, Fales et al., 2008).

3.3 Results

3.3.1 Behavioural Results

In order to assess emotion regulation ability, affect ratings were obtained from each participant on each trial. For sad trials, the 2 (Group) X 2 (Instruction) ANOVA revealed no main effect of group [$F(1,36)=0.042$, $p > 0.8$]. However, a main effect of instruction [$F(1,36)=47.10$, $p < 0.001$] emerged; negative affect ratings were significantly reduced in the regulate relative to attend condition. Importantly, a significant group X instruction interaction was also revealed [$F(1,36)=9.59$, $p < 0.005$; Figure 3.1A] characterized by enhanced regulation of negative emotional reactivity in the CTL group. Follow-up within-group contrasts of the reduce versus attend sad conditions revealed that both the CTL group [$t(18)=-7.11$, $p < 0.001$, two-tailed] and MDD group [$t(18)=-$

2.64, $p < 0.05$] reported significantly less negative reactivity during the regulate condition. A follow-up test of regulation efficacy scores confirmed that the CTL group were significantly more effective than those with MDD at regulating sad affect ($t(36) = 2.05$; $p < 0.05$).

For positive trials, the 2 (Group) X 2 (Instruction: attend positive, enhance positive) ANOVA revealed a main effect of group such that the CTL group rated the scenes as more positive overall [$F(1,36) = 9.08$, $p < 0.005$], and a main effect of instruction such that both groups reported significantly greater positive reactivity when enhancing positive affect [$F(1,36) = 27.91$, $p < 0.001$]. There was also a significant two-way interaction [$F(1,36) = 4.186$, $p < 0.05$, Figure 3.1B], which indicated that the CTL group showed enhanced up-regulation of positive affect. Follow-up within-group contrasts of enhance positive versus attend positive conditions revealed that whereas the CTL group reported a significant increase in positive emotional reactivity [$t(18) = 6.46$, $p < 0.001$], the MDD group's rating of positivity in the enhance condition reflected only a trend [$t(18) = 1.97$, $p = 0.065$, two-tailed]. Lastly, the regulation efficacy score for positive stimuli was significantly greater in the CTL relative to MDD group ($t(36) = 3.01$; $p < 0.005$).

In order to determine whether a relationship existed between regulation efficacy for both the sad and positive emotional contexts, a correlation analysis within each group was performed. This analysis revealed a significant positive correlation between negative and positive regulation efficacy in both the CTL ($r = 0.705$, $p < 0.001$) and MDD groups ($r = 0.631$, $p < 0.005$). Thus, the capacity to regulate negative affect was also associated with more effective regulation of positive affect. Finally, there was no significant relationship between either positive or negative regulation efficacy and depression severity (BDI score; $p > 0.2$) within the MDD group.

3.3.2 FMRI Results

3.3.2.1 BOLD response to trials with sad scenes

We first investigated the BOLD response for trials with sad scenes between groups ($p < 0.005$; $p < 0.05$ FWE corrected; see Table 3.1 for full summary). Irrespective of instruction, sad scenes produced greater activity in an anterior region of vIPFC (BA 10/47) in the CTL relative to MDD group (main effect of group; Figure 3.3A,B). Next, collapsing across groups, we examined the neural response to down-regulate negative affect (main effect of instruction: reduce negative - attend negative; Figure 3.3C-G). Consistent with previous studies of emotion regulation in both healthy and depressed individuals, we found significantly greater activity for the reduce negative condition in left dlPFC (BA 8/9/10) and right dlPFC (BA 10/9), left vIPFC (BA 47/45), left temporoparietal junction (BA 39), and left middle temporal gyrus (BA 21). For the interaction term comparing the two groups in negative affect regulation capacity, [MDD(reduce-attend negative) versus CTL (reduce-attend; Figure 3.3H-K), significant activity was observed in left lingual gyrus (BA 18), right postcentral gyrus (BA 3/4), and right inferior parietal lobe (BA 40/7). The nature of this interaction in all regions was similar: Whereas for the CTL group, attempts to reduce sadness were accompanied by reductions in activity in these regions ($p < 0.05$ in each case), similar attempts were associated with enhanced activity in all these areas for the MDD group ($p < 0.05$ in each case, except the middle occipital gyrus, $p = 0.057$). Notably, for the *a priori* amygdala ROI, an interaction was also observed (Figure 3.3K) whereby CTLs showed greater activity in the attend relative to reduce condition, and patients with MDD displayed the opposite effect. Bar plots of percent signal change for each group and condition can be found in Figure 3.4.

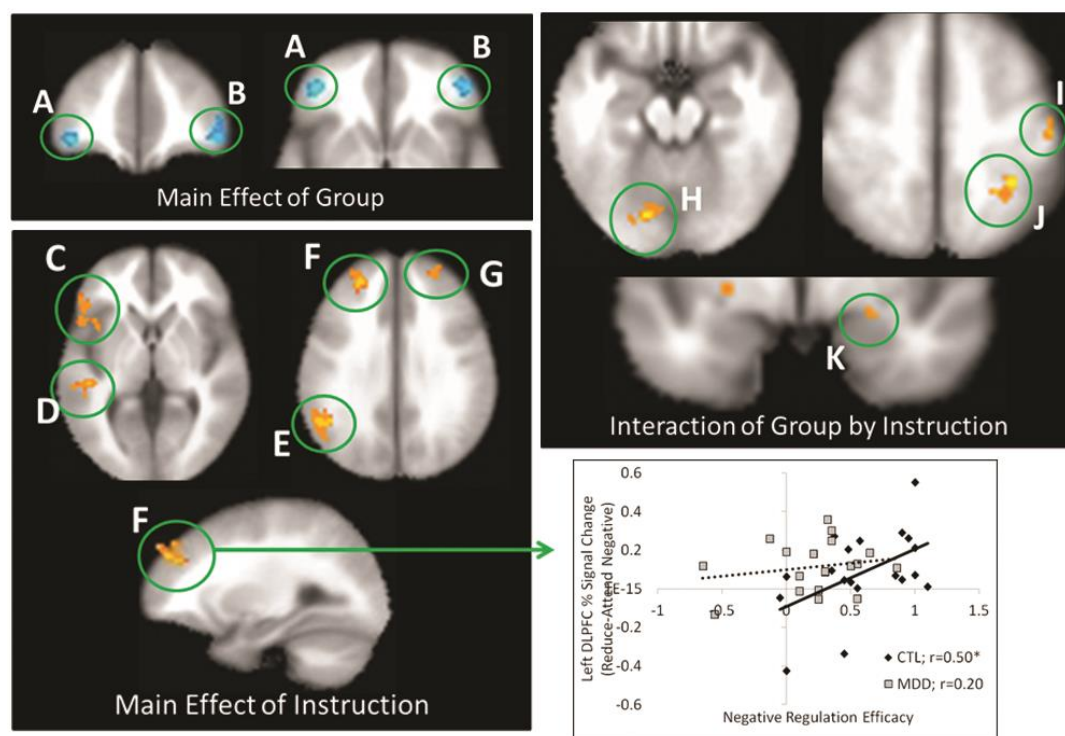


Figure 3.3 BOLD response for the whole brain analysis of negative trials and the relation to regulation efficacy

Top-left – main effect of group demonstrates greater activity in the left (A) and right (B) vIPFC of the CTL relative to the MDD group. **Bottom-left** – Main effect of instruction shows enhanced activity for reduce negative relative to attend negative trials in the (C) left vIPFC, (D) left middle temporal gyrus, (E) left temporoparietal junction, (F) left dIPFC, and (G) right dIPFC. **Top-right** – Group X instruction interaction revealed that whereas brain activity was attenuated in the CTL group on reduce relative to attend negative trials, activity was enhanced in the MDD group within the (H) left lingual gyrus, (I) right postcentral gyrus, (J) right inferior parietal lobe, and (K) right amygdala* (displayed at a thresholded of $p < 0.01$, two-tailed, uncorrected). **Bottom-right** – Negative regulation efficacy was positively correlated with percent signal change in the reduce versus attend conditions in the dIPFC (F) of the CTL group ($p < 0.05$), but not the MDD group ($p > 0.4$). All regions were thresholded at $p < 0.005$, two-tailed, and corrected to $p < 0.05$ (FWE, $k > 47$), except where noted (*). Active clusters are displayed on the

averaged T1-weighted Talairach-Tournoux template (TT_avg152) in AFNI. Refer to Figure 3.4 (below) for bar plots of percent signal change.

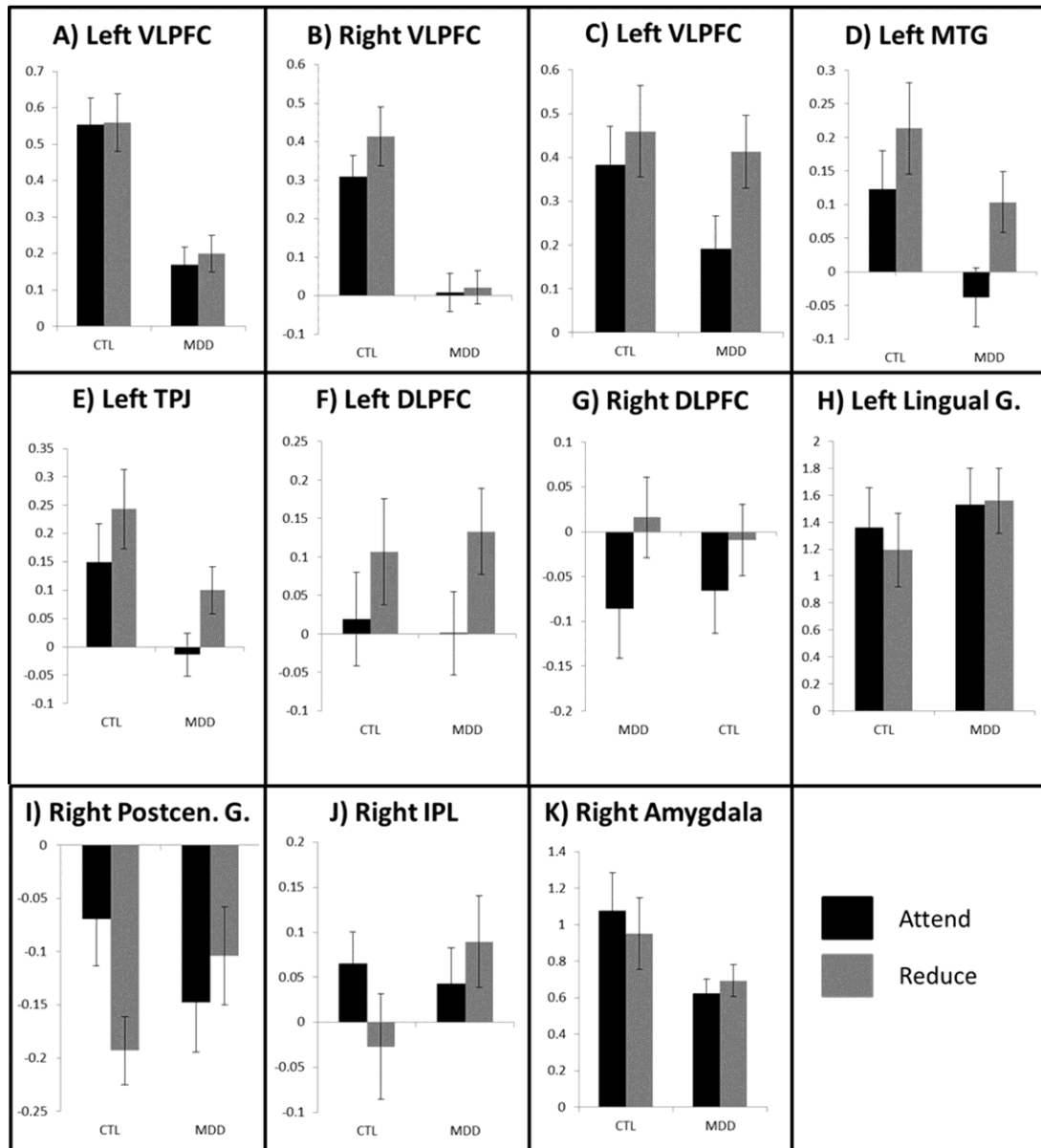


Figure 3.4 Bar plots of percent signal change for fMRI analysis of negative trials

Main effect of group demonstrates greater activity in the left (A) and right (B) vIPFC of the CTL relative to the MDD group. Main effect of instruction shows enhanced activity for reduce negative relative to attend negative trials in the (C) left vIPFC, (D) left middle

temporal gyrus, (E) left temporoparietal junction, (F) left dlPFC, and (G) right dlPFC. Group X instruction interaction revealed that whereas brain activity was attenuated in the CTL group on reduce relative to attend negative trials, activity was enhanced in the MDD group within the (H) left lingual gyrus, (I) right postcentral gyrus, (J) right inferior parietal lobe, and (K) right amygdala.

Table 3.1 Significantly active clusters from the group by instruction analysis of sad conditions

Location	R/L	BA	X,Y,Z	Cluster Size	T-value
<i>Main Effect of Group: CTL (Reduce + Attend Negative) > MDD (Reduce + Attend Negative)</i>					
vIPFC	R	10/47	45,45,-1	81	3.36
vIPFC	L	10/47	-41,41,-4	55	3.65
<i>Main Effect of Instruction: MDD and CTL (Reduce Negative > Attend Negative)</i>					
vIPFC	L	47/45	-48,21,1	152	3.42
dlPFC	L	9/8/10	-28,46,37	166	3.53
dlPFC/Superior Frontal Gyrus	R	10/9	26,48,31	62	3.49
dlPFC/Middle Frontal Gyrus	L	6/9	-40,8,50	57	3.25
Middle Frontal Gyrus	L	6/8	-44,12,59	93	3.59
Superior Frontal Gyrus	R	6/8	16,24,62	84	3.40
Supplemental Motor Area	R/L	6	-4,5,68	410	3.67
Temporoparietal Junction	L	39	-51,-57,23	552	3.73
Temporal Pole/Middle Temporal Gyrus	L	38/21	-51,14,-33	82	3.61
Middle Temporal Gyrus	L	21	-55,-31,-7	140	3.49
Culmen/Cerebellum	R		36,-50,-34	260	3.82
<i>Interaction: MDD (Reduce – Attend Negative) > CTL (Reduce – Attend Negative)</i>					
Precentral Gyrus/Middle Frontal Gyrus	L	6/9	-47,-1,43	72	3.33
Postcentral Gyrus	R	3/4	45,-21,50	70	3.42
Inferior Parietal Lobe	R	40/7	29,-51,53	74	3.51
Precuneus	L	19	-20,-84,32	117	3.38
Cuneus	R	19	30,-82,30	56	3.39
Middle Occipital Gyrus	L	19/18	-36,-86,7	83	3.36
Lingual Gyrus	L	18	-16,-77,30	62	3.35
Amygdala*	R		23,1,-11	14	2.99

The Brodmann location (BA) is provided, along with coordinates for the centre of mass in MNI space (X,Y,Z). Cluster size represents the number of contiguous voxels sharing a face, and the T-value is the mean T-value for all voxels in the cluster. All clusters were

FWE corrected to $p < 0.05$, (uncorrected threshold of $p < 0.005$), with the exception of the amygdala(*) which was thresholded at $p < 0.01$ (uncorrected).

3.3.2.2 BOLD response to trials with positive scenes

We analyzed the BOLD response to trials with scenes that elicit positive affect ($p < 0.005$; $p < 0.05$ FWE corrected; see Table 3.2 for full results). A main effect of group emerged in bilateral dorsomedial prefrontal cortex/supplemental motor area (BA 6), characterized by greater activity in the MDD compared to CTL group. Collapsing across groups, there was significantly greater activity in positive trials during the enhance relative to attend condition (main effect of instruction; Figure 3.5A-G) in bilateral dmPFC/supplemental motor area (BA 6), bilateral anterior VMPFC (BA 10), bilateral perigenual anterior cingulate cortex (pgACC: BA 32/24), left vlPFC (BA 47, extending into superior temporal gyrus), left vlPFC (BA 47, extending into lateral orbital frontal cortex), left temporoparietal junction (BA 39), and right and left ventral striatum. Conversely, there was greater activity in the right dlPFC (BA 9) in the attend relative to enhance condition irrespective of group. Finally, the interaction of MDD (enhance-attend positive) versus CTL (enhance-attend positive) revealed no significant clusters of activity. Bar plots of percent signal change for each group and condition can be found in Figure 3.6.

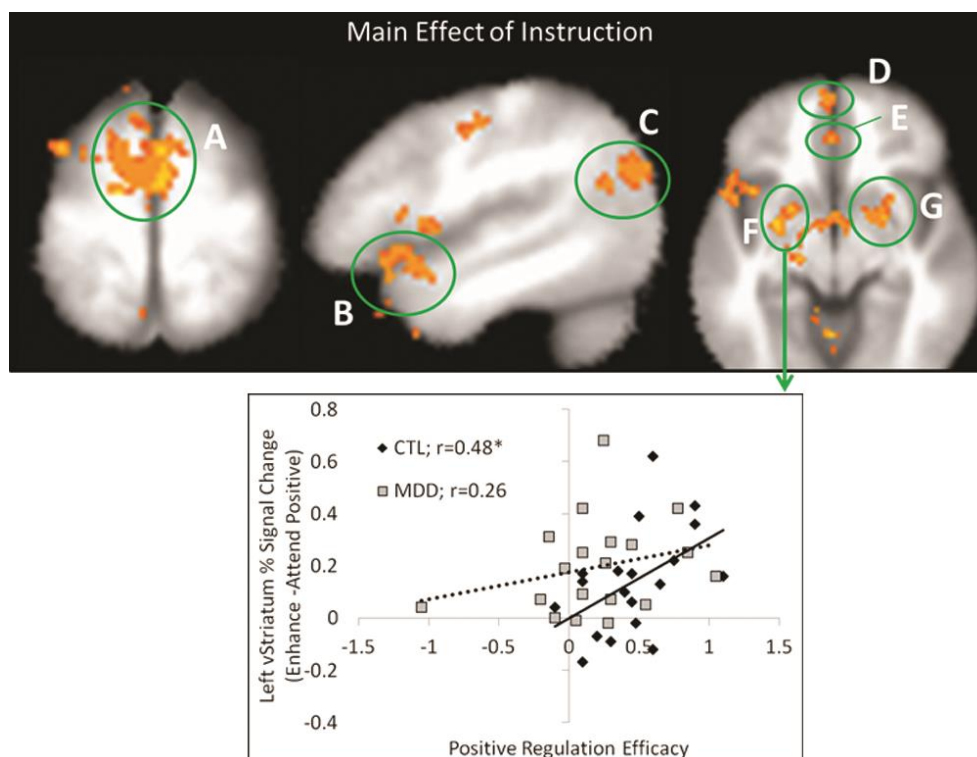


Figure 3.5 BOLD response for the whole brain analysis of positive trials and the relation to regulation efficacy

Top – Main effect of instruction revealed increased activity for enhance positive relative to attend positive trials in the (A) bilateral dmPFC/supplemental motor area, (B) left vIPFC, (C) left temporoparietal junction, (D) bilateral anterior VMPFC, (E) bilateral pgACC, (F) left ventral striatum, and (G) right ventral striatum. **Bottom** – Positive regulation efficacy was positively correlated with the difference in percent signal change between the enhance versus attend positive conditions in the left ventral striatum (F) of the CTL group, but not the MDD group. All regions were thresholded at $p < 0.005$, two-tailed, and corrected to $p < 0.05$ (FWE, $k > 47$). Active clusters are displayed on the averaged T1-weighted Talairach-Tournoux template (TT_avg152) in AFNI. Refer to Figure 3.6 (below) for bar plots of percent signal change.

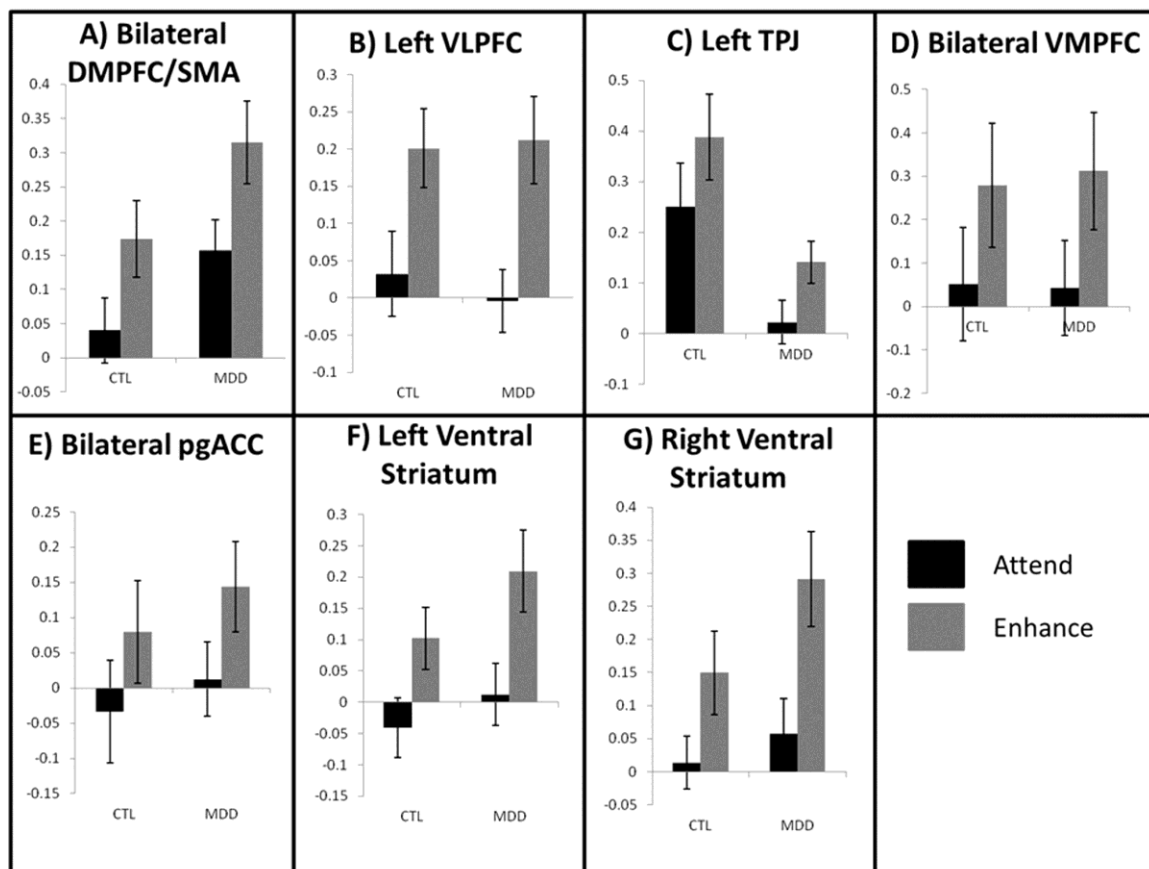


Figure 3.6 Bar plots of percent signal change for fMRI analysis of positive trials

Main effect of instruction revealed increased activity for enhance positive relative to attend positive trials in the (A) bilateral dmPFC/supplemental motor area, (B) left vIPFC, (C) left temporoparietal junction, (D) bilateral anterior VMPFC, (E) bilateral pgACC, (F) left ventral striatum, and (G) right ventral striatum.

Table 3.2 Significantly active clusters from the group by instruction analysis of positive conditions

Location	R/L	BA	X,Y,Z	Cluster Size	T-value
<i>Main Effect of Group: MDD(Enhance + Attend Positive) > CTL (Reduce + Attend Positive)</i>					
dmPFC/Supplemental Motor Area	R/L	6	0,6,56	52	3.46
<i>Main Effect of Instruction: MDD and CTL (Enhance Positive > Attend Positive)</i>					
Superior Frontal Gyrus/Middle Frontal Gyrus	L	8	-19,33,57	111	3.44
Middle Frontal Gyrus/Precentral Gyrus	L	6	-36,1,59	74	3.62
Middle Frontal Gyrus	L	6	-38,10,55	58	3.29
vIPFC/anterior Superior Temporal Gyrus	L	47	-48,15,-11	285	3.48
vIPFC/lateral Orbital Frontal Cortex	L	47	-34,32,-7	95	3.42
vIPFC/Insula	R	44/13	45,4,7	134	3.47
dmPFC/Supplemental Motor Area	L/R	6	-4,-3,65	1027	3.67
Perigenual Anterior Cingulate Cortex	L/R	32/24	-4,39,-2	77	3.56
Anterior VMPFC	L/R	10	-2,60,-4	52	3.43
Insula/Caudate	L	13	-30,8,13	409	3.50
Precentral/Postcentral Gyrus	L	6	-44,-12,41	73	3.31
Superior Temporal Gyrus	R	38	41,21,-29	245	3.53
Temporal Parietal Junction/Middle Temporal Gyrus	L	39	-46,-67,23	369	3.52
Anterior Middle Temporal Gyrus	L	38	-44,12,-33	53	3.47
Precuneus	L	7	-10,-54,49	95	3.50
Parahippocampal Gyrus	L	35	-18,-18,-15	80	3.58
Parahippocampal Gyrus	L	36	-24,-28,-25	50	3.49
Striatum	L		-26,11,10	132	3.53
Ventral Striatum	L		-26,0,-10	128	3.70
Ventral Striatum	R		22,3,-12	108	3.51
Caudate	R		20,11,20	101	3.54
Uncus/Amygdala	R		12,-5,-31	49	3.67
Cerebellum/Lingual Gyrus	R/L		-6,-51,-8	943	3.52
Cerebellum	R		34,-50,-34	291	3.67
Cerebellum	R		22,-27,-33	106	3.61
<i>Main Effect of Instruction: MDD and CTL (Attend Positive > Enhance Positive)</i>					
dIPFC/Middle Frontal Gyrus	R	9	48,19,34	54	3.41
<i>Interaction: MDD(Enhance – Attend Positive) > CTL (Enhance – Attend Positive)</i>					
No Significant Clusters					

All clusters were FWE corrected to $p < 0.05$, (uncorrected threshold of $p < 0.005$). The Brodmann location (BA) is provided, along with coordinates for the centre of mass in MNI space (X,Y,Z). Cluster size represents the number of contiguous voxels sharing a face, and the T-value is the mean T-value for all voxels in the cluster.

3.3.2.3 Comparison of positive and negative regulation

As an exploratory analysis, we compared the regulation of positive (enhance-attend) to the regulation of negative (reduce-attend) directly. This revealed a significant main effect of regulation condition irrespective of group. Specifically, there was greater activity in the MPFC and left ventral striatum during the enhancement of positive scenes, while there was greater activity in the dlPFC and inferior parietal lobe during the regulation of sad scenes. There was no significant group by regulation condition interaction (see Figure 3.7 and Table 3.3 for full results).

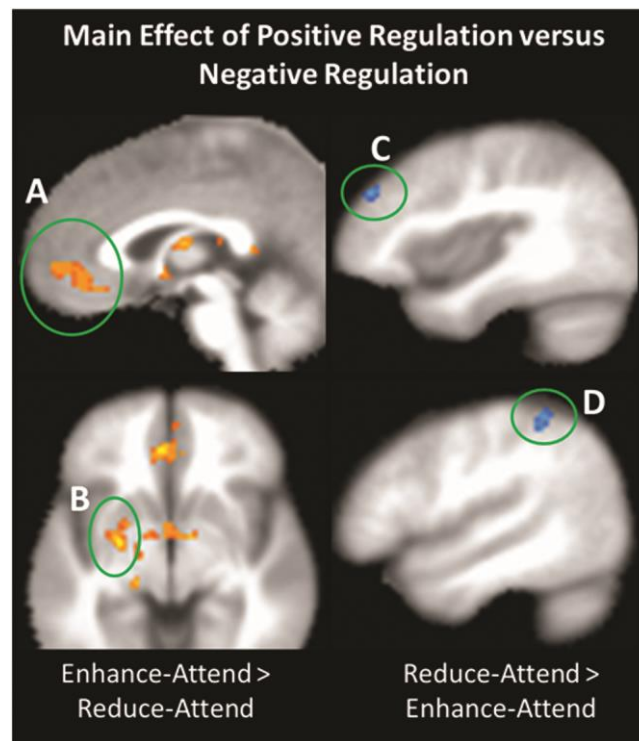


Figure 3.7 BOLD response for the whole brain analysis of the regulation of positive versus the regulation of sad trials

Left – Main effect of regulation condition for “enhance minus attend positive” > “reduce minus attend negative” revealed increased activity in the (A) bilateral MPFC and (B) left

ventral striatum irrespective of group. Right – Main effect of regulation condition for “reduce minus attend negative” > “enhance minus attend positive” revealed increased activity in the (C) left dlPFC and (D) inferior parietal lobe irrespective of group. All regions were thresholded at $p < 0.005$, two-tailed, and corrected to $p < 0.05$ (FWE, $k > 47$). Active clusters are displayed on the averaged T1-weighted Talairach-Tournoux template (TT_avg152) in AFNI.

Table 3.3 Significantly active clusters from the analysis of the regulation of positive versus negative emotions

Location	R/L	BA	X,Y,Z	Cluster Size	T-value
<i>Main Effect of Regulation-type: MDD and CTL [(Enhance-Attend Positive) > (Reduce-Attend Negative)]</i>					
VMPFC/ rostral Anterior Cingulate Cortex	R/L	32	-2,40,-4	187	3.66
Posterior Cingulate Cortex	L	29	-4,-42,3	55	3.72
Precuneus	L	7	-14,-53,42	61	3.61
Cuneus	R	19	26,-88,28	92	3.54
Hippocampus/Parahippocampal Gyrus	L	35	-18,-22,-12	48	3.77
Parahippocampal Gyrus	L	35	-27,-27,-23	47	3.43
Ventral Striatum	L		-26,-5,-10	127	3.78
Thalamus (Pulvinar)	L		-5,-25,10	77	3.50
Thalamus (Medial Dorsal Nucleus)	L/R		-3,-10,10	72	3.53
Hypothalamus	L/R		-1,-2,-7	68	3.47
<i>Main Effect of Regulation-type: MDD and CTL [(Enhance-Attend Positive) > (Reduce-Attend Negative)]</i>					
dlPFC/Middle Frontal Gyrus	R	46/9	42,41,34	48	3.60
Inferior Parietal Lobe	R	40	52,-44,49	83	3.60

All clusters were FWE corrected to $p < 0.05$, (uncorrected threshold of $p < 0.005$). The Brodmann location (BA) is provided, along with coordinates for the centre of mass in MNI space (X,Y,Z). Cluster size represents the number of contiguous voxels sharing a face, and the T-value is the mean T-value for all voxels in the cluster. Note there were no significant Group by Regulation-type interactions.

3.3.2.4 Relationship between brain activity and regulation efficacy

Given that the main effect of instruction for both sad and positive trials revealed recruitment of dlPFC and vlPFC for both groups, we next examined whether there were group differences in the relationship between activity in these regions and regulation efficacy. There was a significant positive correlation between negative regulation efficacy and percent signal change for reduce minus attend negative conditions within dlPFC (Figure 3.3F and bottom right panel) of the CTL [$r = 0.50$, $p < 0.05$, two-tailed] but not the MDD group [$r = 0.198$, $p > 0.4$, two-tailed], and a similar trend within the vlPFC [Figure 3.3C; CTL: $r = 0.45$, $p = 0.056$, two-tailed; MDD: $r = -0.01$, $p > 0.9$, two-tailed]. For positive trials, we found no significant within group correlations in either dlPFC or vlPFC regions. However, given the role of the ventral striatum in reward processing and that dysfunction in this region is thought to contribute to depression (Pizzagalli et al., 2009), we performed two additional correlations in the ventral striatum clusters identified by the main effect of instruction. A significant positive correlation between positive regulation efficacy and percent signal change for enhance minus attend positive trials emerged in the left ventral striatum of the CTL but not the MDD group [Figure 3.5F and bottom panel; CTL: $r = 0.48$, $p < 0.05$, two-tailed; MDD: $r = 0.26$, $p > 0.2$, two-tailed]. There was a similar trend for the right ventral striatum [Figure 3.5G; CTL: $r = 0.40$, $p = 0.09$, two-tailed; MDD: $r = 0.25$, $p > 0.3$]. One possibility is that the null correlation result in depressed patients could be attributed to restricted variance. To examine this possibility, an F-test of equality of variance was performed. This test indicated that this null finding could not be explained by unequal variance between groups for either negative regulation efficacy scores ($p > 0.5$) or positive regulation efficacy scores ($p > 0.1$). It is important to note, however, between group comparisons of the r -values (Fisher r -to- z) and regression slopes identified in these analyses reveal no significant between group differences ($p > 0.1$, all two-tailed).

3.3.2.5 Relationship between brain activity and depression severity

Two whole-brain analyses were performed within the MDD group to determine whether depression severity, as indexed by the BDI, correlated with the magnitude of BOLD change from regulate-minus-attend conditions (one for sad trials, the other for

positive trials). This revealed no significant clusters of activity after correcting for multiple comparisons.

3.4 Discussion

The current study adapted experimental emotion regulation techniques to reflect elements of cognitive theory and associated psychotherapies in order to delineate neurocognitive abnormalities associated with modulating the negative cognitive triad in MDD. Although the CTL group was significantly better than depressed patients at regulating both positive and negative affect, evidence was also observed for the successful regulation of sad affect, and to a lesser extent, positive affect in participants with MDD. The capacity to regulate negative affect was highly correlated with the capacity to regulate positive affect. At the neural level, significantly greater recruitment of dlPFC and vlPFC during the regulate versus attend negative stimulus condition was observed in both groups; however, a significant correlation between brain activity and subjective indices of regulation success existed only in CTLs. Additionally, a group by instruction interaction revealed that only CTLs exhibited reduced activity in regions implicated in the representation of sensory information and emotional encoding. For example the amygdala, and visual areas known to respond more robustly to emotionally significant stimuli (Ishai et al., 2004, Lindquist et al., 2012, Padmala and Pessoa, 2008, Padmala and Pessoa, 2011, Pessoa et al., 2002, Vuilleumier et al., 2001). Similarly, during positive affect enhancement, we observed recruitment of vlPFC and dmPFC in both groups. We also observed increased activity in neural regions associated with reward and emotionally salient stimulus encoding, particularly bilateral regions of ventral striatum; however, only in controls was activity in this region significantly correlated with ratings of positive affect. The results provide partial evidence that a dissociation exists in depressed patients between activity in neural regions associated with emotional control and encoding, and indices of regulation success.

3.4.1 Neural regions for the control of emotion

In the current task, both groups exhibited a similar increase in activity of dorsal PFC regions and vLPFC while regulating both sad and positive affect. These neural regions are widely implicated in healthy emotion regulation (Mitchell, 2011, Mitchell and Greening, 2012, Ochsner and Gross, 2005, Ochsner et al., 2004). One means by which dlPFC is thought to exert emotional control is via an attention-related amplification of goal-specific or alternate representations in occipito-temporal cortices, which compete in an inhibitory fashion with emotional representations (Blair and Mitchell, 2009, Mitchell, 2011). It has also been suggested that dorsal regions of prefrontal cortex are involved in explicit reasoning about how emotional associations can be changed (Ochsner and Gross, 2005), or are involved in the neural representation of social and emotional processes (Moll et al., 2005, Wood and Grafman, 2003). In addition, dorsal regions might reduce activity in emotion-related brain areas such as the amygdala via second-order connections with MPFC (Delgado et al., 2008). It has been suggested that vLPFC is involved in updating the representation of optimal motor responses (Greening et al., 2011, Mitchell et al., 2009), in the active regulation of an emotional response (Phan et al., 2005, Wager et al., 2008), or in updating the representation of the optimal motor and emotional responses (Kringelbach and Rolls, 2003, Mitchell, 2011). In line with these ideas, lesions to lateral areas of dlPFC (relative to medial PFC) are associated with increased vulnerability to depression (Koenigs et al., 2008), and activity in both dlPFC and vLPFC has been associated with regulation success in healthy controls (Phan et al., 2005, Wager et al., 2008). The current study demonstrated, however, that despite both groups showing similar patterns of activation in dlPFC during negative affect regulation, only in the CTL group was this activity significantly correlated with regulation efficacy. This finding should be interpreted with caution, however, as the follow-up comparisons of the two correlations revealed no significant between group differences. Notably, this type of between group comparison of correlations can suffer from low power (Yarkoni, 2009), and so larger sample sizes are required to address this question. Furthermore, relative to individuals with MDD, negative affect regulation in the CTL group was associated with significantly reduced activity in neural regions associated with encoding emotional sensory information, including visual areas, and the amygdala (Padmala and Pessoa,

2008, Padmala and Pessoa, 2011). Together with the behavioural results, the current findings suggest that appropriate levels of prefrontal cortex activity may exist in patients with MDD without commensurate relief of negative affect or reductions in sensory encoding of negative stimuli. The results of the current study are consistent with each of the models of dlPFC and vlPFC discussed above, and suggest that these regions are involved in the modulation of emotional stimuli and not simply response suppression. Further work is required to determine whether the reduced efficacy is associated with dysfunction in outputs of emotion-related brain areas targeted by PFC, or due to abnormalities in the nature of the computations performed by PFC during emotion regulation. For example, PFC activity in patients may be disproportionately devoted to representing task-demands or conflict rather than being allocated to performing executive control over emotion. Alternatively, the modified context formed during emotion regulation may be represented in PFC, but varies in emotional content between groups (Moll et al., 2005).

The current study is only the second to examine the online enhancement of positive affect in patients with MDD, and the first to relate activation to indices of regulation success. Significantly enhanced activity in left vlPFC, dmPFC, and regions of dlPFC was observed during attempts to up-regulate positive affect. Similar increases in activation during this condition were also observed in both groups in the ventral striatum. However, only in the CTL group was this enhancement significantly correlated with regulation success. Interestingly, this region is believed to be a target of PFC regions like vlPFC during emotion regulation (Peters et al., 2009, Wager et al., 2008). The current results are consistent with suggestions that emotion-related abnormalities within the striatum are implicated in depression (Epstein et al., 2006, Robinson et al., 2012, Heller et al., 2009, Osuch et al., 2009, Bluhm et al., 2009). They are also consistent with previous research showing that greater dlPFC and vlPFC activation to emotional cues prior to a course of CBT was positively correlated with treatment success (Ritchey et al., 2011). When enhancing positive emotion, irrespective of group, we also observed a cluster in vlPFC that included a small part of anterior superior temporal lobe. In depression, generalized self-blame has been found to be associated with functional connectivity disruption between the anterior superior temporal lobe and regions of the

subgenual anterior cingulate cortex (Green et al., 2012). This raises the possibility that reappraisal involves modifications to the representation of self-concepts, a process that is ineffective in depression (Beck et al., 1979).

3.4.2 Limitations

This study utilizes a standard explicit emotion regulation paradigm in depressed patients that incorporated strategies from cognitive theories of depression and associated psychotherapies. It is important to acknowledge the limitations that any laboratory-based task has as an approximation of the therapeutic context. CBT involves training over many sessions. Furthermore, the stimuli used in the present study to trigger an emotional response were standardized images rather than autobiographical or idiosyncratic cues (Eddington et al., 2009, Lemogne et al., 2009), which is an important consideration given evidence that different stimuli can yield distinct effects (Siegle et al., 2007, Kross et al., 2009). Additionally, we have no direct means of assessing task compliance in the current task. It is possible that rumination by the depressed group might have impaired their ability to employ the regulation strategy throughout the entire trial (Levens et al., 2009). Nevertheless, it is notable that the current emotion regulation strategy modulated neural areas previously shown to be affected in patients following a formal treatment course with CBT (e.g., Goldapple et al., 2004, Jensen et al., 2012). Moreover, patients also reported significant down-regulation of negative affect, and a near significant up-regulation of positive affect.

3.4.3 Conclusion

The current study raises the possibility that depression is not associated with a failure to recruit neural regions implicated in the regulation of emotion, but rather, that the recruitment of such regions is less effective in modulating subjective emotional states and activity in emotional and sensory brain areas. Because activity in regions associated with cognitive control was appropriate in depressed patients, these results are also consistent with suggestions that depression is associated with significant regulatory efforts over negative affect without commensurate relief (Farb et al., 2010, Segal et al., 2006). This may explain why depression can persist in the presence of normal (e.g.,

Beauregard et al., 2006), excessive (e.g., Johnstone et al., 2007), or reduced (e.g., Erk et al., 2010) recruitment of areas associated with emotion regulation. Further work is required to determine whether the reduced efficacy is due to abnormalities in the nature of the computations performed by PFC (e.g. impaired cognitive control, Siegle et al., 2007) or due to dysfunction in the output of emotion-related regions targeted by PFC. Nevertheless, the current study highlights the potential use of neuroimaging to test the efficacy of existing or novel therapies (De Raedt et al., 2010, Linden, 2006), and also the need to delineate potential synergistic interactions between different pharmacological interventions and psychotherapies.

3.5 References

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CHAPTER 4

4 A network of amygdala connections predict individual differences in trait-anxiety³

Abstract

In this study we demonstrate that the pattern of an amygdala-centric network contributes to individual differences in trait-anxiety. Using maximum likelihood estimates of amygdala connectivity to multiple brain targets derived from probabilistic tractography on 72 participants, we could predict trait-anxiety significantly above chance. The prediction was performed using a stratified six-fold cross validation procedure using a regularized regression model from machine learning, the elastic net. This analysis also revealed a reliable network of regions implicated in the prediction model. This included positive contributions from parietal and occipitotemporal regions implicated in attention and perception, and negative contributions from regions implicated in extinction learning such as medial orbitofrontal cortex (mOFC), and reward-related behaviour, including nucleus accumbens (NAcc). The current study provides novel insight into a possible mechanism responsible for information processing biases observed in disorders of emotion, while also confirming the inclusion of prefrontal mechanisms of emotion regulation.

³ Chapter 4 is submitted as: Greening, SG, Mitchell, DGV (Submitted). A network of amygdala connections predict individual differences in trait-anxiety

4.1 Introduction

Anxiety-related disorders are the most prevalent mental illnesses (Kessler et al., 2005a, Kessler et al., 2005b), and high trait-anxiety is associated with increased risk for numerous mental disorders, including depression and bipolar disorder (Bruckl et al., 2007, Reinherz et al., 2000). Neurocognitive models of anxiety highlight the importance of the amygdala (Davis, 1992, Rauch et al., 2003), and interactions with regions of cognitive control, emotion regulation, and perception (Bishop, 2007, Milad and Quirk, 2012). Despite its relevance to affective disorders, little is known about the relationship between trait-anxiety and the integrity of structural connections between these systems. Functionally, individual differences in trait-anxiety are negatively correlated with medial orbitofrontal cortex (mOFC) activity, and positively correlated with amygdala activity during fear modulation (Indovina et al., 2011). Furthermore, functional connectivity between the amygdala and mOFC is negatively related to temperamental anxiety (Kim et al., 2011, Pezawas et al., 2005). Thus, robust amygdala-mOFC connectivity may be protective for anxiety. Conversely, enhanced functional connectivity between amygdala and perceptual regions during fear-generalization is positively correlated with trait-anxiety (Dunsmoor et al., 2011). Moreover, high trait-anxiety is associated with enhanced activity to fear-related cues in sensory cortices or visual areas (Etkin et al., 2004), which is thought to be driven by interactions between these regions and the amygdala (Vuilleumier et al., 2004). One possibility is that high trait-anxiety is associated with enhanced structural connectivity between amygdala and regions involved in perception.

Only two studies to date have examined the relationship between measures of structural white-matter and individual differences in anxiety. Kim and Whalen (2009) demonstrated that functional anisotropy (FA; a measure of white-matter microstructure) in a region of putative uncinate fasciculus extending to nucleus accumbens (NAcc), is negatively correlated with trait-anxiety. More recently, in a large multi-cohort study, Westlye et al. (2011) found that FA throughout much of the white-matter skeleton was negatively correlated with harm avoidance. Despite these contributions, it remains unknown whether a more distributed pattern of structural connections between the

amygdala in particular and other neural regions are related to individual differences in trait-anxiety.

To address this unknown, the present study is the first to combine a multiple regression analysis using a regularized model from machine learning, known as the elastic net (Zou and Hastie, 2005), with maximum likelihood estimates of structural connectivity of the amygdala using seed-based probabilistic tractography (Behrens et al., 2007, Behrens et al., 2003). This powerful approach allows for the identification of structural connections between the amygdala and multiple brain regions in a whole-brain manner (Saygin et al., 2011, Saygin et al., 2012). After first ensuring that the pattern of amygdala structural connectivity could be used to significantly predict individual differences in trait-anxiety, we sought to determine which connections were most reliably included in the prediction model. Thus, we tested the intriguing possibility that trait-anxiety would not only be associated with reduced connectivity between the amygdala and emotion control regions like mOFC, but also enhanced structural connectivity between amygdala and the sensory cortex pathways responsible for driving emotion perception.

4.2 Methods

4.2.1 Participants

Seventy-two healthy right-handed participants [mean age = 25.5 ± 6.5 (SD), median age = 24; 41 females and 31 males; no significant difference in age between sexes ($p > 0.5$)] provided trait anxiety scores [mean = 30.6 ± 7.7 (SD), median = 29, range 21 to 63; MWomen = 29.8 ± 6.4 (SD), MMen = 31.6 ± 9.2 (SD); no significant difference in trait-anxiety between sexes ($p > 0.3$)] by completing the State-Trait Anxiety Inventory (STAI; Spielberger, 1983) and completed a diffusion-weighted imaging (DWI) scan. All participants were in good health, and had no history of psychiatric illness, neurological disease, or head injury as determined by screening and interview using the Structured Clinical Interview of the DSM-IV (First et al., 2002). All participants provided

informed written consent, and the study was approved by the research ethics board of the University of Western Ontario.

4.2.2 Data acquisition

Diffusion-weighted and T1-weighted imaging was performed on a 3-Tesla Siemens MRI scanner with a 32-channel head coil at Robarts Research Institute, University of Western Ontario. DWI images were acquired in the axial plane with echo-planar imaging consisting of 55 slices, 2.1 x 2.1 x 2 mm voxels, 200 x 200 mm field of view, 96 x 96 mm base resolution, 65 isotropically weighted diffusion directions, b-value = 700 s/mm², repetition time 6 sec, and echo time 75 msec. The high-resolution T1-weighted anatomical scan covered the whole brain (repetition time = 2300ms, echo time = 4.25 msec; field of view = 25.6 cm; 192 slices; 1 mm³ isovoxels; 256 x 256 matrix).

4.2.3 Segmentation and Probabilistic Tractography

Relevant to the current study, the validity and utility of probabilistic tractography has recently been demonstrated in two studies of amygdala segmentation (Bach et al., 2011, Saygin et al., 2011), and another study predicting individual differences in functional activation in fusiform gyrus (Saygin et al., 2012). We first performed these analyses with the right amygdala as the seed region, and then followed up with an investigation of the left amygdala as seed. However, we had no strong predictions of laterality a priori given that meta-analyses of functional data have failed to find robust evidence for generalized lateralization of function (Sergeyev et al., 2008, Wager et al., 2003). Seed and target masks were defined using the cortical and subcortical automated segmentation tools in FreeSurfer (Fischl et al., 2002, Fischl et al., 2004) using the T1-weighted anatomical images of each participant. This produced an individually derived amygdala seed mask and 86 target masks, which included masks of the contralateral amygdala, 84 additional unilateral regions and one bilateral region (brainstem), all of which were visually inspected for quality control. Prior to probabilistic tractography, the

DWI data were eddy current corrected, skull stripped, and the principal diffusion directions of each voxel were determined (Behrens et al., 2007). Probabilistic tractography was carried out in each participant's native diffusion space using FSL-FDT (Behrens et al., 2007) in which 25,000 sample tracts were drawn from each voxel in the amygdala seed region, which produced a frequency distribution of connecting tracts to each target while avoiding a mask of the ventricles (Saygin et al., 2012, Saygin et al., 2011). The maximum likelihood of amygdala-target connectivity was derived by taking the value of the amygdala voxel with the largest number of sample tracts connecting to the respective target and dividing by 25,000 (producing a scaled value between 0 and 1). This method was adopted as the preferred approach given its use in functional neuroimaging studies of anxiety, which use the voxel of peak activity for individual differences analyses (Bishop, 2009, Bishop et al., 2007). In this manner, the maximum likelihood estimate was determined for each of the 86 amygdala-target combination for each of the 72 participants (observations), which produced a matrix of 72 observations by 86 features for performing multiple regression.

4.2.4 Multiple Regression analysis

Multiple linear regression was implemented using an elastic net model using the scikit-learn toolbox in python (Pedregosa et al., 2011). Elastic net is a regularized regression model for sparse data, and was selected for use in the current study because it is robust to instances in which the number of features is greater than the number of observation and there is collinearity between features (Zou and Hastie, 2005). Elastic net appears to outperform the other regularized regression models of least absolute shrinkage and selection operator (LASSO) and ridge regression by combining the strengths of each. Elastic net creates a parsimonious model by forcing the least informative weights to zero, thereby producing a regression model comprised of non-zero and zero weights. Thus, regularization identifies a subset of features important to the model and the magnitude of their respective weights. The value of alpha was set to 0.5 for all analysis, representing a fifty-fifty compromise between ridge regression (i.e., all non-zero weights) and the extreme sparsity preferred by LASSO (i.e., few non-zero weights). The regularization parameter,

lambda, was determined using an automated internal cross-validation function, `elasticnetCV`, and was different for the right and left amygdala analyses. Though the amygdala appears highly connected to ipsilateral regions of the prefrontal cortex, temporal lobe, and subcortical regions (Ghashghaei et al., 2007, Zikopoulos and Barbas, 2012), the assumption of sparsity in our data required by the regression model is supported by evidence from tract tracer studies in primates. These have demonstrated amygdala connections are largely unilateral (Ghashghaei and Barbas, 2002) and thus relatively sparse compared to the number of features included in our analysis. In order to assess whether the regression model could significantly predict trait-anxiety scores we used a stratified six-fold cross-validation approach (see Figure 4.1 for a schematic). Similar to previous application of sparse regression in neuroimaging (Wager et al., 2011), a stratified six-fold approach was selected as it tends to have a prediction accuracy biased towards zero (i.e., is more conservative), and produces more consistent (i.e., less variable) results relative to leave-one-out cross-validation (Kohavi, 1995, Hastie et al., 2009). We performed six iterations in which we split the data, trained the regression model on 60 participants and tested on the remaining 12 participants (see Figure 4.1). The data was split such that no participant was ever included in the training and testing set simultaneously, no participant was in more than one of the six test sets, and there was a similarly distributed range of trait-anxiety values at each fold. Concatenating the 12 predicted anxiety scores from each fold produced a vector of 72 predicted anxiety scores, one predicted score for each participant. The accuracy of the predictions was measured by computing the mean squared error (MSE) between the predicted and actual trait-anxiety scores. To determine the statistical significance of the connectivity model accuracy for predicting anxiety we used random permutation testing. For this we performed 1000 permutations samples, each time randomly pairing observations with a trait-anxiety score. The p-value was determined as the proportion of iterations in which a model generated on the randomized data outperformed or was equal to the model generated on the real data. Finally, we ran the analyses described above with sex included as an additional feature and found that for neither the right nor left amygdala seed region was the prediction accuracy improved.

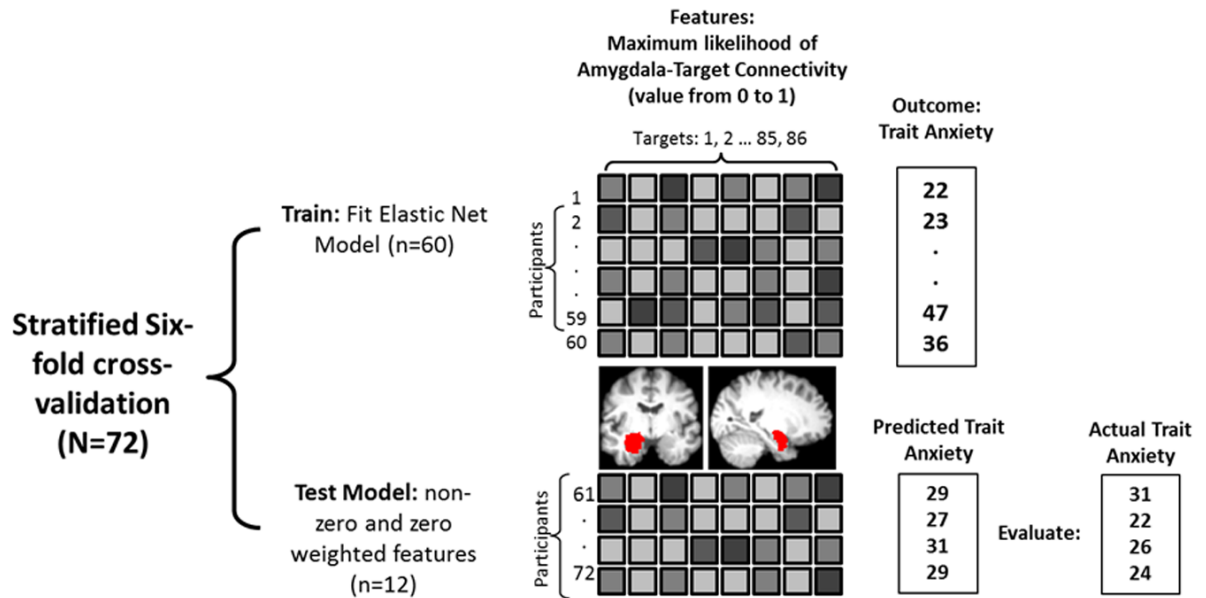


Figure 4.1 Schematic of the multiple regression approach

Participants were split using a stratified six-fold cross validation approach, producing six independent training (n=60) and testing (n=12) sets. The regression model was trained on the scaled values of the maximum likelihood of amygdala-target connectivity derived from probabilistic tractography (between 0 and 1, represented as the grey-scaled boxes). Testing the model at each fold produced predicted trait-anxiety scores for 12 participants. The accuracy of the model was derived by computing the MSE between the 72 predicted trait-anxiety scores and actual trait-anxiety scores provided by self-report.

4.2.5 Full-Model Estimation

In order to determine which features (i.e., which amygdala-target anatomical connections) made a reliable contribution to a full-model for predicting individual differences in anxiety we adapted the bootstrap procedure used by Wager et al. (2011). We performed 1000 bootstrapped samples with replacement, which produced training sets of 60 observations. In this fashion, we derived 1000 independent models and their respective weights. To assess the reliability we counted the number of times that a given feature made a non-zero contribution to the full-model across the 1000 bootstraps. We

then performed 10×10^6 randomized permutations of the data, each time performing 1000 bootstraps, thereby producing a distribution of the likelihood (i.e., the number of times out of 1000) a given feature would make a non-zero contribution to a full-model due to chance. The p-value was determined as the proportion of iterations in which a model generated on the randomized data produced a number of non-zero weights for a given feature greater than or equal to the number produced by the bootstrap on the real data. The resulting p-values were then compared to a Bonferroni adjusted alpha of 0.0019 ($0.05/26$) to correct for multiple comparisons, which was derived from the number of features that had a non-zero weight at any iteration of the 1000 bootstraps drawn from the real data. An estimation of which amygdala-target connections made the most reliable contribution to the full-model is extremely relevant to the neuroscience of anxiety, though it must be noted that predictions are necessarily made from the combination of all weights across all non-zero features (Wager et al., 2011) and are therefore not strictly independent. We also calculated the mean value of the weights across all iterations of the bootstrap for each amygdala-target connection making a reliable contribution to the full-model. Notably, all distribution of weights across the 1000 bootstraps were non-Gaussian, due to the over-representation of zeros produced by the sparse regression model on iterations where the given feature was excluded from the model. For these reasons, estimations of central tendency were not used to assess the reliability of each feature, but are provided for informational purposes (see Table 4.1).

4.3 Results

4.3.1 Model Testing

The elastic net model ($\alpha = 0.5$; $\lambda = 0.3246$) trained on the maximum likelihood of amygdala-target connectivity for the right amygdala performed significantly better than chance at predicting trait-anxiety ($p < 0.05$, two-tailed, Figure 4.2). While the MSE of trait-anxiety estimates was 57.965, the mean MSE from the randomized permutation samples was 60.515. However, the model did not perform better than chance using connectivity patterns of the left amygdala ($\text{MSE} = 59.06$, $p > 0.08$). This was true

when using the parameters derived using automated cross-validation ($\alpha = 0.5$; $\lambda = 120.27 \times 10^{11}$) and when using those from the right amygdala analysis.

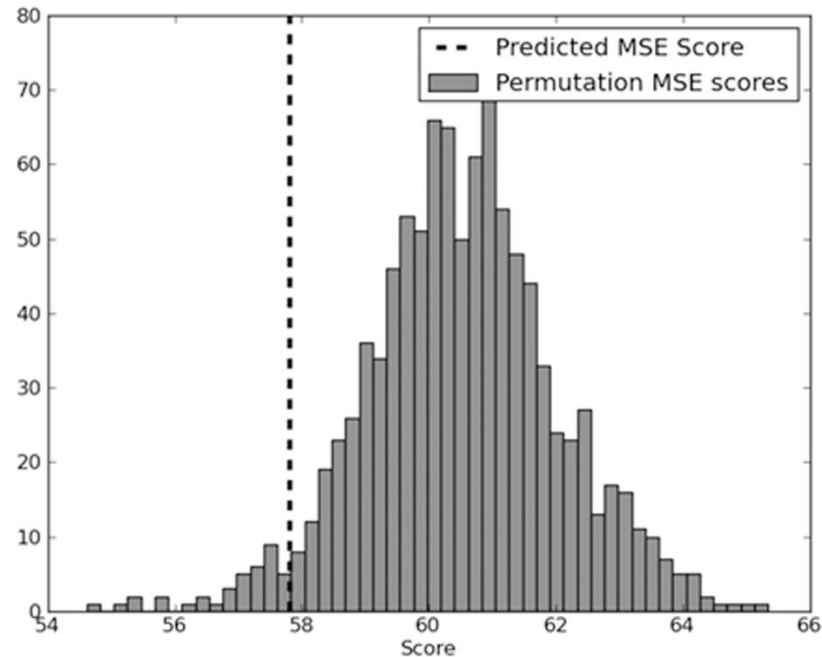


Figure 4.2 Results of permutation testing on the right amygdala

Permutation testing with 1000 iterations revealed that the regression model predicts trait-anxiety significantly better than chance. The dashed line represents the prediction accuracy of the model across the six-folds reported as MSE. The solid grey bars represent the MSE permutation scores. The number of permutations within a given bin of the histogram is found on the y-axis, while the MSE for the bins is presented along the x-axis.

4.3.2 Full-model estimation

Given that an elastic net model could predict trait-anxiety significantly better than chance from probabilistic connectivity profiles of amygdala-target pathways of the right amygdala, a critical question was which pathways makes the most reliable contribution to a full-model (see Table 4.1 & Figure 4.3). Notably, our full-model estimation revealed that the reliable pathways with positive weights included right inferior temporal gyrus

(ITG), lingual gyrus, supramarginal gyrus (SMG), superior parietal lobe (SPL), postcentral gyrus, precentral gyrus, bilateral thalamus, and left hippocampus. This result suggests that stronger anatomical connectivity between the amygdala and these regions is associated with reduced trait-anxiety. Those reliable pathways with negative weights included right nucleus accumbens (NAcc) and middle temporal gyrus (MTG), and bilateral medial orbitofrontal cortex (mOFC). This suggests that reduced anatomical connectivity between the amygdala and these regions is associated with increased trait-anxiety.

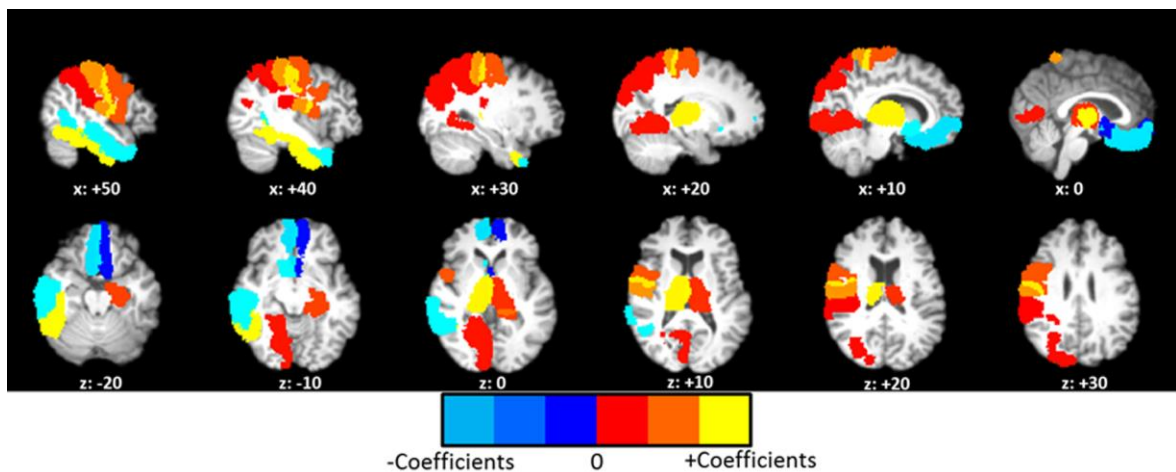


Figure 4.3 Features making the most reliable contribution to a generalized full regression model for predicting trait-anxiety

Sagittal (top) and axial (bottom) slices are displayed along with the respective MNI intercept. The estimated weight for each target region implicated can be found in Table 1.

Table 4.1 Targets of structural connectivity with right amygdala that make a reliable contribution to the full-model for predicting trait-anxiety

Target	Weight (mean)	<i>p</i> -value
<u>Significant positive predictors of trait-anxiety</u>		
R Inferior temporal	1.9091	<0.000001
R Thalamus	0.2274	<0.000001
R Postcentral	0.1384	<0.000001
R Precentral	0.0773	0.000027
L Hippocampus	0.0595	<0.000001
L Thalamus	0.0428	<0.000001
R Lingual	0.0176	<0.000001
R Superior Parietal	0.0088	0.000063
R Supramarginal	0.0005	0.000077
<u>Significant negative predictors of trait-anxiety</u>		
R Nucleus Accumbens	-0.5108	<0.0000010
R Middle Temporal	-0.5094	<0.0000010
R Medial Orbitofrontal	-0.4542	0.0005230
L Medial Orbitofrontal	-0.0152	0.0001490

4.4 Discussion

Using a combination of probabilistic tractography and a regularized multiple regression model from machine learning, known as the elastic net, the current study is the first to demonstrate that the pattern of amygdala structural connectivity is sufficient to predict individual differences in trait-anxiety. Furthermore, consistent with our prediction and relevant to the understanding of neurocognitive models of anxiety, emotion, and emotion regulation more generally, the current results revealed that a reliable network of multiple structural pathways connected with the amygdala is involved. Connections with the amygdala making a positive contribution to predicting trait-anxiety comprised target regions implicated in perception and attention to sensory cues (Farb et al., 2013, Mitchell and Greening, 2012), including right inferior and superior temporal, lingual, superior parietal, supramarginal, and postcentral gyri, as well as bilateral thalamus. Conversely, regions making a negative contribution to the model are those implicated in extinction learning, such as bilateral mOFC, and reward-related processing, including right NAcc, respectively (Ballard and Knutson, 2009, Milad and Quirk, 2012). Although prior studies have identified pathways that show a negative correlation with trait-anxiety, our study is the first to identify pathways wherein enhanced connectivity is positively related to trait-anxiety.

4.4.1 Regions making a positive contribution to trait-anxiety

The strength of amygdala connectivity to multiple occipitotemporal regions implicated in sensory perception/ventral visual stream processing (Amaral, 2002) was positively associated with trait-anxiety. The target regions for these pathways included inferior temporal cortex, superior temporal cortex, and lingual gyrus. Emotional face processing is associated with enhanced functional connectivity between amygdala and similar visual areas (Pessoa et al., 2002, Morris et al., 1999). Interactions between the amygdala and sensory cortices are also associated with anxiety. For example, increased functional connectivity between the amygdala and visual cortices has been found in response to phobia-related photos (Ahs et al., 2009), and in response to traumatic scripts

in individuals with post-traumatic stress disorder (Gilboa et al., 2004). Enhanced visual cortex activity to negative visual cues has also been found in other disorders, particularly depression (Surguladze et al., 2005, Fu et al., 2008), which is highly comorbid with anxiety (Barlow, 1991, Kessler et al., 2005b).

It is interesting to consider these results in the context of recent models of emotion perception, and cognitive biases in affective disorders. It is thought that excitatory interactions between the amygdala and sensory regions enhance representations of emotional stimuli (Vuilleumier and Driver, 2007, Anderson and Phelps, 2001, Mitchell and Greening, 2012). In affective disorders, however, emotional thoughts or stimuli disproportionately affect cognition, producing 'efficient but maladaptive' (pg. 971, Beck, 2008) information processing biases. Thus, one possibility is that in highly anxious individuals, persistent functional connectivity between these regions strengthens anatomical connections with perceptual and attentional areas, possibly via Hebbian mechanisms. In this manner, emotions exert an even stronger influence on sensory processes, cognition, and behaviour. Alternatively, the strength of such connections may represent an inherited trait, predisposing affected individuals to increased risk of psychopathology. These strengthened connections may pose a particular challenge for attempts to regulate emotion. For example, it was recently demonstrated that, despite attempts to down-regulate negative affect, depressed patients had persistently elevated activity in the amygdala and sensory areas, including occipital, parietal, and somatosensory cortices (Greening et al., 2013). Thus, our results, and recent experimental evidence, provide novel insight into the importance of amygdala-occipitotemporal connections, a pathway that has been overlooked in current neurocognitive models of psychopathology.

A number of regions implicated in attentional control (Corbetta and Shulman, 2002) were also included in the model, such as right superior parietal lobe and right supramarginal gyrus. This finding may account for the attention-related difficulties in highly anxious individuals, and more generally, the robust impact of emotional distracters on aspects of cognition (Mogg and Bradley, 2005). Functionally, behavioural impairments produced by emotional distracters appear related to enhanced amygdala

activity along with suppressed activity in frontoparietal regions (Dolcos and McCarthy, 2006, Mitchell et al., 2008). Our findings appear to suggest that stronger amygdala-parietal connections are associated with higher trait-anxiety, in accordance with the observed functional antagonism between these areas.

The current findings also highlight the potential importance of attention-related therapies in the management of affective disorders (Amir et al., 2009). For example, previous research has demonstrated that sensory processing of emotion can be down-regulated indirectly through attention-related mechanisms (Mitchell et al., 2008, Mitchell et al., 2007). It is thought that this occurs because attention augments the representation of non-emotional task-relevant stimuli in occipitotemporal cortices, thereby leading to the suppression of unwanted, possibly pathological, emotional representations (Mitchell, 2011, Blair and Mitchell, 2009).

4.4.2 Regions making negative contribution to trait-anxiety

We observed that the strength of connectivity between the amygdala and mOFC was negatively related to trait-anxiety. This is consistent with findings in both rodents and humans suggesting that the mOFC regulates amygdala output during extinction learning (Milad and Quirk, 2012). Recent neuroimaging studies suggest an inverse relationship between activity in the amygdala and medial prefrontal cortex, including mOFC, during the modulation of fear-related stimuli (Amting et al., 2010, Linnman et al., 2012). This pattern is impaired in patients with anxiety disorders (Etkin et al., 2010, Shin et al., 2005). Intriguingly, a recent resting state connectivity study demonstrated that individuals low in trait-anxiety displayed positively correlated activity in amygdala and mOFC (Kim et al., 2011). Both Westlye et al. (2011) and Kim and Whalen (2009) similarly identify that white-matter in mOFC and NAcc areas was negatively related to anxious traits. In sum, the present results and other finding support the conclusion that strong functional and structural connectivity between amygdala and mOFC is protective from anxiety.

Consistent with recent findings concerning reward behaviour, amygdala-NAcc connectivity was negatively associated with trait-anxiety. Stuber et al. (2011) demonstrated that activation of an amygdala-NAcc pathway stimulated reward-seeking, suggesting that these connections facilitate non-anxious behaviour. In patients with depression, deep brain stimulation of the NAcc reduces symptoms of anxiety (Bewernick et al., 2010). Moreover, functional studies have demonstrated the importance of interactions between the amygdala and NAcc in modulating emotion processing (Peters et al., 2009, Wager et al., 2008). The current findings raise the possibility that reward-related connections between the amygdala and NAcc represent an anxiolytic pathway distinct from connections between amygdala and mOFC.

4.4.3 Implications for models of anxiety

Although the current work involved an examination of anxiety in a non-clinical sample, our findings also appear consistent with those from studies of patients with anxiety disorders. Consistent with our finding that amygdala-mOFC connectivity was negatively related to anxiety, the most frequently reported finding in anxiety disorders is reduced FA in regions of the uncinate fasciculus (Baur et al., 2011, Hetttema et al., 2012, Phan et al., 2009, Tromp et al., 2012). Thus, the current approach provides important information regarding the specificity of structural connections to the amygdala and their role in anxiety and affective disorders more broadly. It is important to note that probabilistic tractography is agnostic to whether connections are first-order or higher. It is therefore possible that the connections described between the amygdala and the given target regions are indirect. Recent models of emotion control do indeed implicate such indirect pathways in the modulation of amygdala function (Delgado et al., 2008, Mitchell, 2011, Blair and Mitchell, 2009). It is also likely that multiple anatomical risk factors contribute to individual differences in anxiety and emotional reactivity. The current study demonstrated that an amygdala-centric network may represent one such risk factor. It is possible that use of alternative seed regions could yield other important pathways, as suggested by previous whole-brain DWI studies (Baur et al., 2011, Hetttema et al., 2012). The approach used in the present study could be adapted in the future to examine the

pattern of connectivity of other structures previously implicated in anxiety, (e.g, middle frontal gyrus, Bishop, 2009), which did not factor into the current model. Finally, the current evidence regarding laterality is equivocal and requires future research, as our findings implicated right amygdala, while others emphasize either left (Kim and Whalen, 2009), or bilateral (Westlye et al., 2011) amygdala connections in trait-anxiety.

4.4.4 Conclusion

The current findings demonstrate that trait-anxiety can be predicted from structural connectivity patterns of the right amygdala. For the first time, we show that trait-anxiety is positively related to the strength of structural connectivity between the amygdala and a distributed set of brain regions implicated in perception, attention, and behaviour, including inferior and superior temporal, occipital, parietal, somatomotor, and somatosensory cortices. Thus, the findings provide evidence that individual differences in structural connections may underlie the information processing biases observed in dysregulated affect. Critically, both amygdala-mOFC and amygdala-NAcc connectivity was negatively related to trait-anxiety, emphasizing the importance of interactions between these structures in modulating anxiety and fear. Future work is needed to determine whether individual differences in the identified network arise during development (e.g., via Hebbian mechanisms), represent a congenital risk factor, or both. The present study also provides a novel approach for predicting individual differences from patterns of structural connectivity which can be applied in a multitude of domains within cognitive neuroscience.

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CHAPTER 5

5 General Discussion and Future Directions

The three presented studies provide novel insight into the processes of emotional flexibility. Together they represent a complimentary approach, which includes between-group comparisons of individuals with MDD and healthy controls, individual differences analyses, and multiple brain imaging modalities (fMRI and DWI). In general, these studies highlight the benefit of studying psychiatric disorders for both improving our understanding of the disorders themselves, and for bettering our understanding of the underlying neural substrates of basic cognitive processes. Furthermore it emphasizes the utility of applying cognitive paradigms first established in healthy participants to the study of psychiatric disorders. This general discussion will begin by highlighting the main findings as they relate to emotional flexibility. This will also include discussions of the limitations and possible future directions of the work undertaken. Specifically, the general discussion will attempt to integrate important findings from all three experimental chapters while discussing first emotional reactivity, and second emotion control. The final section will discuss the implications of the findings for models of MDD. Specifically, the final section, “toward a neurocognitive model of MDD”, will discuss why the neural regions involved in perception deserve consideration in models of MDD, and how such perceptual process relate to emotional flexibility.

5.1 Emotional reactivity

The first two studies revealed important information regarding the amygdala and emotional reactivity. We investigated between group differences in emotional reactivity, which involved both determining how socio-emotional cues compete for neural representation in the amygdala and how effortful emotion regulation modulates amygdala activity. This line of research demonstrated that heterogeneity in the pattern of amygdala activity in patients with MDD is also influenced by variability in task-demands. These findings are interpreted with respect to current theories regarding information processing

in MDD. We also observed significant emotional modulation of the visual and sensory regions, which the DWI study (Study 3) demonstrated was more strongly connected with the amygdala in highly anxious participants.

5.1.1 The amygdala and reactivity to negative and positive emotions

In the first study we observed that task-demands, whether or not an emotional facial expression was presented centrally (task-relevant) or peripherally (task-irrelevant), influenced how the amygdala responded. The amygdala's response to task-relevant faces was different in participants with MDD versus controls. There was greater activity for the MDD group for fearful faces but less activity for happy faces relative to controls. However, the same pattern was not present when emotions were task-irrelevant, in which case there was reduced amygdala activity for happy faces in the MDD group, but no significant differences between groups for fearful distracters. In Study 2, we identified a cluster within the amygdala displaying attenuated activity in controls during the down-regulation of negative scenes; however, this region displayed increased activity in the MDD group during the same condition. Broadly, our findings are consistent with a growing body of research demonstrating that amygdala activity can vary from one moment to the next as a function of the goals of the organism and the situational context (Stokes et al., 2009b, Cunningham and Brosch, 2012, Cunningham et al., 2008). Indeed, Cunningham et al. (2008) recently demonstrated that in the same sample of participants, the amygdala responded preferentially to negative images when the task objective was to focus on negativity, yet preferentially to positive images when asked to focus instead on positivity. Thus, task- or goal-demands necessarily have an impact on amygdala reactivity.

There is also data to suggest that an additional source of heterogeneity in amygdala reactivity is the stage of development of the participants. Todd et al. (2011) recently demonstrated that early in development children have greater amygdala reactivity to happy relative to angry faces; though in young adults there was no difference

in amygdala response. This observation suggests that amygdala reactivity can vary as a function of development, and is also indicative of a positive emotional bias early in development. While these findings are relevant to the discussion of the neural regions involved in emotional reactivity specifically, they also represent an important future direction for the study of emotional flexibility more generally. Thus, an expressed need for future work into the development of these processes will be reiterated in later sections. Specifically, moving forward from cross-sectional and cohort designs, longitudinal research is needed to examine the functional and structural changes that take place over time and how these changes might contribute to emotional flexibility and psychopathology.

5.1.2 Emotion reactivity, amygdala, and MDD

With respect to MDD and related cognitive models of depression, our findings highlight that task goals can influence indices of emotional reactivity, including amygdala activity and self-reported measures of emotional feelings. The amygdala findings in Study 1 indicate that task-relevant, but not task-irrelevant, emotional cues are processed in a manner consistent with the negative-bias. On the other hand, in Study 2, MDD participants rated the negative scenes as producing an emotional reaction similar to controls (i.e., not more negative, as might be predicted). In terms of amygdala activity in Study 2, when asked to reduce negativity the MDD group displayed an increase in amygdala activity, though controls had reduced activity (group by condition interaction). The MDD group also had less amygdala activity overall to negative scenes (though not significant). These latter findings appear inconsistent with the negative-bias. Instead they are at least partially consistent with emotion context insensitivity, which would predict blunted emotional reactivity to negative cues along with the observations of reduced reactivity to positive cues (though the positive effects would be predicted by both cognitive models). Overall, the findings are most consistent with studies in healthy controls demonstrating that task-demands can modulate amygdala reactivity (Bishop et al., 2007, Pessoa et al., 2002, Vuilleumier et al., 2001, Cunningham et al., 2008). Furthermore, they suggest that the inconsistent findings regarding amygdala activity in

depressed patients are influenced not only by heterogeneity between patient samples (e.g., between group variability in sub-threshold mania, Fournier et al., 2012), but also by the task goals and/or the experimental context. For example, we speculated in Study 1 that in order for a pattern of amygdala activity consistent with the negative-bias to arise it needs to be spatially attended. In this manner, spatial attention may be one cognitive factor mediating the negative-bias, which works by biasing the representation of emotional cues. Similarly, others have suggested that depression is associated with the impaired ability to disengage attention from negative task-irrelevant cues only after they are attended (De Raedt and Koster, 2010, Mogg and Bradley, 2005). Future work which explicitly manipulates spatial attention to emotional and non-socio-emotional stimuli is needed to substantiate this interpretation of the current findings.

5.1.3 Additional future direction for the study of emotional reactivity

An important limitation of the functional results regarding emotional reactivity is that we are unable to ascribe the functional changes observed in the amygdala to more specific nuclei. Recently, Saygin et al. (2011) demonstrated that probabilistic tractography could be used to segment the amygdala into four regions: lateral, basal, central, and medial aspects. This approach could be combined with scan parameters optimized for scanning the amygdala at higher resolution, and allow for the investigation of functional differences between sub-regions of the amygdala. Such an approach has been shown to be effective at demonstrating the persistent representation of fear-conditioning in the segmented amygdala (Bach et al., 2011). However, Bach et al. (2011) only segmented the amygdala into two sub-regions (superficial and deep). Nevertheless, this type of approach could, for example, prove useful in distinguishing activation in lateral regions of the amygdala, which appear to receive perceptual information, versus activation of central amygdala, which has afferent connections to brainstem structures involved in autonomic arousal (LeDoux, 2012, Cunningham and Brosch, 2012; see also Figure 1.2).

5.2 Emotion control

Regarding emotion control, the present studies uncovered a number of interesting and novel findings. Regarding the involvement of vmPFC, we observed that it was particularly active during the up-regulation of positive emotions (Study 2), while stronger vmPFC-amygdala connections predicted lower trait-anxiety (Study 3). We also found that the brain regions implicated in emotion regulation (e.g., vIPFC, dlPFC, and dmPFC) were recruited when a neutral face was task-relevant and fearful distracters were present in the visual field (Study 1), or when participants attempted effortful reappraisal of positive or negative emotions (Study 2). These findings suggest that these regions are involved in both direct and indirect forms of emotion regulation (i.e., reappraising emotional significance versus attending to non-emotional tasks or distraction). Furthermore, in addition to the role of the vIPFC in emotion regulation, evidence indicating that the vIPFC may also contribute to a form of 'reflexive' emotion control will be discussed (Hooker and Knight, 2006).

5.2.1 Implications for the vmPFC

Only in Study 2 did we observe functional activation of the vmPFC. In that experiment vmPFC was more active during attempts to enhance positive emotional reactivity regardless of group (main effect of regulation). Interestingly, activity in this region during attempts to enhance positivity was significantly greater than during attempts to down-regulate negative emotions, regardless of group. This is not necessarily as predicted given the supposed role of vmPFC in the 'reflexive' down-regulation of the amygdala during the suppression of negative emotion. Based on previous research, we had predicted greater activity in vmPFC in the controls relative to MDD participants during the presentation of negative scenes (possibly irrespective of condition). Instead, the observed finding may be consistent with recent reviews highlighting that the vmPFC

is comprised of a number of distinct sub-regions (Myers-Schulz and Koenigs, 2012, Ray and Zald, 2012). Consistent with the findings of study 2, Myers-Schulz and Koenigs (2012) suggest that the more anterior parts of vmPFC contribute to positive emotional states in particular. Nevertheless, Study 3 demonstrated that strong connections between the amygdala and vmPFC predict low trait-anxiety, which supports interpretations of this region being important in the healthy modulation of emotion-related behaviour (Schiller and Delgado, 2010).

Future work is required to disentangle the relative contributions of the various sub-regions of vmPFC. One way of performing segmentation in an *a priori* fashion would be to use the segmentation techniques that use probabilistic tractography, which were discussed previously. Recent evidence has demonstrated the ability of this approach to segment regions such as the frontal pole (Liu et al., 2013), premotor cortex (Tomassini et al., 2007), and parietal lobe (Wang et al., 2012) anatomically, and that regions identified in this manner appear functionally dissociable. It should also be noted that, similar to research regarding the functional activation of the amygdala throughout development (Todd et al., 2011), the functional relationship between the amygdala and the vmPFC appears to vary as a function of developmental stage (Gee et al., 2013). Whereas a positive functional relationship is observed in response to fearful faces in participants between four and nine years old, for groups between 10 and 22 these regions are inversely related.

5.2.2 Emotion regulation: direct, indirect, and (possibly) 'reflexive'

Regarding direct, emotion-focused, emotion regulation (i.e., reappraisal, refer to Figure 1.1) we found functional evidence supporting the role of dorsal and lateral parts of the prefrontal cortex in these processes. Our findings appeared contradictory to some, yet consistent with other evidence from previous studies of emotion regulation in MDD. Specifically, in Study 2 we observed that during the CBT-based reappraisal (i.e., effortful and direct emotion regulation) of both negative and positive scenes there was increased activity for both control and MDD participants in parts of the lateral and dorsal prefrontal

cortex, including: dlPFC, dmPFC, and vlPFC. However, despite similar neural activity in these cognitive control regions, healthy controls, relative to the MDD patients, displayed significant modulation of their self-reported emotional response. Furthermore, during trials with negative scenes, only in controls did we observe that dlPFC activity positively correlated with the effectiveness of emotional down-regulation. Moreover, only in controls did we observe attenuated activity in the amygdala and sensory/perceptual regions during down-regulation. This suggests that relative to controls, patients with MDD can similarly employ CBT-type strategies, though they do not experience the same reduction in emotional reactivity. Our findings appear somewhat contradictory to other studies regarding MDD and the down-regulation of negative emotional scenes. Specifically, while Johnstone et al. (2007) found greater dlPFC activity in patients relative to controls, Erk et al. (2010) found greater dlPFC activity in controls relative to depressed participants. Regarding the up-regulation of positivity, in both groups we found increased activity in the vlPFC, dmPFC, and parts of dorsal prefrontal cortex, though behaviourally controls were significantly better at enhancing positivity. Notably, only in controls was the magnitude of regulation efficacy for positive scenes positively correlated with activity in ventral striatum/nucleus accumbens. This is consistent with previous research demonstrating that reduced functional connectivity between dlPFC and the ventral striatum was found in depressed and not control participants (Heller et al., 2009), which appears to improve with antidepressant treatment and predicts increased positivity (Heller et al., 2013). However, the dlPFC identified in this study does not appear to precisely overlap with regions we identified. With regards to both negative and positive regulation, it is possible that the use of different emotion regulation strategies in each study accounts for the functional differences observed between studies (e.g., Goldin et al., 2008). Future work could extend previous studies using healthy normal subjects by studying multiple forms of direct and/or indirect emotion regulation strategies within a single sample of depressed and control participants (e.g., McRae et al., 2010, Kanske et al., 2011, Goldin et al., 2008).

In Study 1 we also observed that the controls had greater activity in an anterior portion of the vlPFC, relative to participants with MDD, when negative facial expressions were presented in the visual field but were distracting from task-goals. We speculated

that, relative to the MDD participants, peripheral negative faces were more distracting for controls, which necessitated greater recruitment of the cognitive control regions in order to maintain behavioural performance. If true, this might suggest that in controls emotional reactivity was modulated in an effortful and indirect manner (i.e., spatial attention was voluntarily directed away from the emotional faces) when attending to a neutral stimulus with fearful distracters. More specifically, the frontoparietal regions, which include both PFC and parietal regions, associated with attention appear to have been recruited to maintain task-related representations and ignore the salient distracters (e.g., McRae et al., 2010, Kanske et al., 2011).

An alternative, and not mutually exclusive, possibility is that the vIPFC displays some degree of reflexivity such that its inhibition-related activity can occur without being instructed to do so (i.e., without effortful attempts to modulate the emotional response) (Hooker and Knight, 2006). Notably, in study 2 we found that bilateral clusters in the anterior vIPFC were more active in controls than depressed participants for negative scenes regardless of the instruction (i.e., main effect of group). This is consistent with previous observations. For example, Vuilleumier et al. (2001) found that bilateral vIPFC was active whenever fearful faces were present, regardless of whether they were attended or ignored, as did Mitchell et al. (2008) in the presence of negative distracters regardless of whether or not there was a cognitive task to perform. Bishop et al. (2004) also demonstrated that the magnitude of vIPFC activity during blocks of frequent fearful face distracters was negatively correlated with individual differences in state-anxiety. Speculatively, activity in the vIPFC may partially reflect a degree of reflexive emotion control that is involved in the unconscious inhibition of, and protection from, unwanted emotional reactions (e.g., Lieberman et al., 2007). Furthermore, this pattern of vIPFC reflexivity may be in addition to its parametric response during effortful emotion regulation (i.e., it has an initial all-or-none response which later increases proportionately to the amount of effort) (Payer et al., 2012). Alternatively it may indicate that there are functionally dissociable sub-regions of the vIPFC (i.e., anterior versus posterior sub-regions similar to those in Study 2). Recent work has demonstrated that vIPFC can be functionally segregated based on various cognitive processes (Hampshire et al., 2012), though future work is required to determine how putative functional division of vIPFC

might be implicated in emotion control more specifically. Nevertheless, an important caveat to an interpretation of reflexive anterior vIPFC for the clusters in Study 2 is that we did not control for the possible confound that healthy controls were voluntarily controlling their emotions during the attend condition despite being instructed not to. In the future, we could account for this confound by having participants report if they were performing uninstructed emotion regulation in a follow-up interview. For example, during particularly negative scenes, the control participants may have diverted their attention towards benign features of the scene more so than depressed participants. We could corroborate this self-reported data by tracking and measuring the participants' eye gaze during these trials.

5.2.3 Additional future direction for the study of emotion control and MDD

Moving forward, it has recently been recommended that emotion regulation processes, specifically reappraisal, be examined using an effective connectivity approach (Ray and Zald, 2012). Effective connectivity is an elaborate form of functional connectivity that allows for a mediation (or path) type analysis such that it measures how some nodes within a network contribute to the activation variance of other nodes in that network (Chen et al., 2011). Thus, the use of effective connectivity would allow for further inferences regarding how regions of the dorsal and lateral prefrontal cortex are interacting with the amygdala and the regions involved in perception and sensation (e.g., early visual cortical areas). For example, using a mediation-style analysis Johnstone et al. (2007) found that in controls the vmPFC mediated the down-regulation of amygdala activity by the vIPFC, but in depressed participants the vIPFC had no significant effect on vmPFC activity. However, an effective connectivity model could be used to test a larger network, which would include additional nodes in the network. For example, this approach could be used to determine if the reduction of amygdala activity observed in controls during reduce-negative conditions is best accounted for by direct functional pathways with vIPFC, or via indirect pathways involving dlPFC-vIPFC-occipitotemporal

connections, or both. We could then compare this information to the MDD group to determine if there are significant differences in specific functional pathways.

In general, we interpreted the findings discussed in this section to support models of emotion regulation, which suggest that cognitive control regions of the frontoparietal cortices, including dlPFC, vlPFC and IPL, modulate emotional reactivity by activating competing sensory representations in occipitotemporal cortex (Bishop, 2007; Mitchell, 2011). The next section will elaborate on this framework. Specifically, the following section will discuss in more detail how the emotion control and emotional reactivity findings converge to provide novel insight into neurocognitive models of major depression.

5.3 Toward a neurocognitive model of MDD

While a number of important, informative, and largely overlapping, neurocognitive models depression exist (Phillips et al., 2003, Price and Drevets, 2010, Roiser et al., 2012), the present findings, along with other research, indicate that they remain incomplete. This section will expand on one facet of emotion processing that has largely been left out of current neurocognitive models of MDD. Specifically, the involvement of the processes of perception, sensation, and their related cortices will be discussed in the context of emotional processing. This will be referred to as emotion perception. The inclusion of emotion perception is argued to provide novel insight into the psychopathology of emotion disorders, and is an additional step forward in our understanding of these disorders. Furthermore, these perceptual brain regions are a potentially important node within which the processes of emotional reactivity and emotion control can directly interact. The evidence for this will be discussed in the context of schema-based cognitive models of emotional disorders.

The schema-based cognitive model of depression (Beck et al., 1979) and anxiety (Beck and Emery, 1985) is the most influential and widely employed framework for both the understanding and treatment of emotional disorders, particularly depression and

anxiety. Schemas have been succinctly described as "enduring structural representations of human experience... that direct the identification, interpretation, categorization and evaluation of experience" (pg. 419, Clark and Beck, 2010). In disorders of emotion, negative schemas form a robust and intertwined organization with many facets of cognition due to their repeated activation. It is thought that this process renders the negative schemas easier to activate, possibly by reducing the threshold or intensity of stimuli required to activate them (Clark and Beck, 2010). This process is believed to account for information processing biases observed in disorders of emotion, including the negative-bias observed in MDD (Beck, 2008). However, where and how are the negative cognitive schemas encoded in the brain? Despite the use of terms such as "structural representations" in the explanation of negative cognitive schemas, it remains unclear how the development of maladaptive schemas relate to structural or functional aspects of the brain.

To date, favored models implicate the amygdala as the primary locus of the negative-bias (Beck, 2008). However, this work has tended to disregard possible interaction between the amygdala and regions involved in perception and sensation. In Study 2, we observed that while the control group displayed reduced activity in brain regions implicated in visual perception and somato-motor processing during conditions requiring the down-regulation of negative emotional reactivity, the MDD group displayed increased activity in these regions. Similarly, our DWI findings in Study 3 found that strengthened connectivity between amygdala and regions of occipitotemporal and parietal areas was related to high trait-anxiety. Much research in patients with MDD has demonstrated a potentiated response in visual cortical regions to negative emotional cues (Davidson et al., 2003, Fu et al., 2004, Fu et al., 2008, Surguladze et al., 2005), which appears reduced following treatment with either CBT (Fu et al., 2008) or antidepressants (Fu et al., 2004). Furthermore, the opposite pattern is observed in response to positive cues, such that participants with MDD have a reduced response to happy faces in visual cortex (Surguladze et al., 2005), and greater recovery following antidepressant treatment is associated with greater visual cortex activity in response to happy faces (Fu et al., 2007). This suggests that the negative-biases and related schemas, while involving and perhaps requiring the amygdala early on in emotional learning, can arise from at least two

complimentary mechanisms involving the perceptual and sensory cortices. The first involves strengthened *structural connections* between the amygdala and regions of emotion perception. The second involves the *restructuring* of the occipitotemporal cortices involved in aspects of perception, sensation, and semantic representations (Haxby et al., 2000, Martin, 2007, Ungerleider, 1995) such that they produce a potentiated response to emotional information that requires little, or no, amygdala involvement.

Regarding evidence for strengthened structural connectivity between the amygdala and regions of emotional perception, past research in rhesus monkeys has demonstrated direct anatomical connections between the amygdala and the striate and extrastriate cortices implicated in visual perception (Amaral, 2002). Moreover, in humans with amygdala lesions there is a significant decrease in the amount of extrastriate cortex activity relative to the amount normally observed in response to emotional facial expressions (Vuilleumier et al., 2004). There is also evidence from rodent models of fear and reward conditioning demonstrating, using lesions or electrophysiology, that there is encoding of emotional significance within the primary perceptual cortices of audition (Jarrell et al., 1987, Teich et al., 1988) and vision (Chubykin et al., 2013, Shuler and Bear, 2006). Speculatively, these pathways are strengthened throughout development via Hebbian mechanisms, in a “fire-together, wire-together” fashion. One possibility is that the process of rumination, in which individuals with depression experience perseverative negative thoughts (Nolen-Hoeksema et al., 2008), facilitates this process by providing repeated activation. For example, when participants are asked to imagine visual cues in the absence of stimulation there is robust and significant activity in these regions (Stokes et al., 2009a, Ishai et al., 2002), which may suggest a possible neural mechanism whereby ruminative behaviour potentiates the neural pathways relating to negative representations within emotion perception regions (e.g., Cooney et al., 2010, Kross et al., 2009). An alternative possibility is that robust structural connectivity between the amygdala and perceptual areas is an inherited trait. Future longitudinal studies involving both functional and structural measures of connectivity between these regions are needed to determine if one or both of these possibilities accounts for present observations. Nevertheless, in this manner perceptual biases for negative stimuli appear to arise as a result of input to the

perceptual cortices from the amygdala (Todd et al., 2012), though likely in a reciprocal network-type array.

An additional possibility is that negative cognitive schema are also the result of cortical restructuring and neuronal plasticity within the perceptual cortices, such that these regions become more sensitive to schema-congruent stimuli. This process is likely complimentary to observations of strengthened connectivity between the amygdala and the regions for emotion perception, as an increase in sensitivity could facilitate the integration of emotional information into the relevant neural networks. Although there is reasonable evidence to suggest that changes to the perceptual brain regions reflects efferent activation from the amygdala (Vuilleumier et al., 2004), there is also evidence from animal models suggesting that early perceptual brain regions are necessary for the long-term retention and expression of emotion encoding (e.g., fear conditioning, Jarrell et al., 1987, Teich et al., 1988). In studies of non-human primates, the amygdala appears necessary for the acquisition, but not the retention of fear conditioning (Antoniadis et al., 2007, Antoniadis et al., 2009). Furthermore, there is evidence of cortical plasticity in early sensory cortices of both animal models (Headley and Weinberger, 2013) and humans (Thiel et al., 2002) during auditory fear conditioning. The existence of such cortical restructuring following emotional learning might suggest that, once learned, perceptual biases can arise early in perceptual processing without, or with limited, input from the amygdala. Thus, along with previous observations, the current findings (particularly Study 2) may reflect persistent and long-term changes to the perceptual and sensory cortices via mechanisms of neural plasticity. It should be noted that such changes do not preclude the involvement of amygdala connections and related neural networks, given that the amygdala appears to be necessary for the rapid acquisition of such learned emotional associations (Antoniadis et al., 2007, Antoniadis et al., 2009) and subsequent cortical plasticity (Weinberger, 2004, Weinberger, 2007). Future work is needed to determine if facilitated cortical plasticity might be an additional risk factor for the negative-biases observed in disorders of emotion. Notably, in a recent study involving individuals with social anxiety disorder, Doehrmann et al. (2013) were able to significantly predict treatment outcome (patients were treated with a course of CBT) based on only the visual cortex activity of patients in response to emotional faces. This

study employed a cross-validated multiple regression approach from machine learning, similar to the approach used in Study 3. Although neither study examined long-term changes, a similar approach could be used to identify differing functional cognitive biases and how they might change over time. For example, one possibility is that greater amygdala-occipitotemporal connectivity is an inherited characteristic from which we can predict the likelihood that either anxiety or depression will develop, yet only after experience-related plasticity can visual cortex activity to negative cues be used to predict the development of emotional disorders.

5.3.1 Interactions between emotion perception and emotion control

The importance of these perceptual brain regions is further emphasized given that they are robustly modulated by the frontoparietal regions involved in attention and cognitive control. There is much evidence demonstrating that attention and cognitive control can drastically effect the neural representation of stimuli within the perceptual and sensory cortices (e.g., Kastner et al., 1998, Kastner and Ungerleider, 2000, de Fockert et al., 2001, Rees et al., 1997). Based on this work, current models of emotion regulation (e.g., Blair and Mitchell, 2009) have suggested that the mechanisms responsible for the modulation of emotional representations are those of top-down biased-competition. As such, the models suggest that contributions from frontoparietal cortices modulate the regions of the occipitotemporal cortices (e.g., extrastriate cortex, including occipital and inferior temporal cortices; see also Figure 1.3). On the other hand, the tuning of emotion perception regions and/or related networks in such a manner that they come to prefer negative cues might account for the observation in Study 2. Specifically, although patients with MDD recruited frontoparietal regions during direct emotion regulation of negative cues, there was no modulation of activity in perceptual brain regions. This may suggest either that the regions of dlPFC and vlPFC have impaired functional connectivity to the regions of emotion perception, the strength of negative presentations was such that the impact of reappraisal strategies was ineffectual, or some combination of both.

In terms of treatment, this model of emotion perception may suggest that CBT, and related treatments, may work by improving the ability of cognitive control regions involved in emotion regulation to activate goal-relevant representations in perceptual brain regions. If so, this would have the effect of suppressing the negative representations which would have been preferentially activated. An additional possibility is that this work has implications for the use of either computerized attention-based therapy in treating MDD (Browning et al., 2012), similar to the type shown to be affective at treating anxiety disorders (Amir et al., 2009), or imagery-based bias modification interventions (Holmes et al., 2009). Such treatments may facilitate the strengthening of connections between regions like dlPFC and vlPFC to those involved in emotion perception. It would be interesting to determine if such an approach prior to (or along with) CBT would help overcome the apparent functional disconnection or ineffectiveness we observed in Study 2. Notably, treating patients with a full course of CBT may produce a similar effect; however, the use of attention-related therapy is an intriguing possibility due to its potential low cost and ease of implantation, as it is computer based, rather than clinician based, and could be used outside of a clinical setting.

5.3.2 Additional future direction for neurocognitive models of MDD

Throughout the breadth of research covered in this discussion an important and reoccurring future direction involves the role of development versus inheritance in the processes of emotional flexibility. This includes discussions regarding models of MDD and emotion perception. The current data included patients who had already developed major depression, thus we are unable to determine whether the observed neural correlates represent risk-factors or a symptom of MDD. Future work is required to determine how the findings regarding emotion dysfunction in MDD develop. This is true for patterns of emotional reactivity in the amygdala, for patterns of functional and structural connectivity between vmPFC-amygdala during emotion control, and for structural connectivity between amygdala-occipitotemporal cortices involved in emotion perception. Thus, future work could assess whether the changes in either/or function and

structure occur overtime, whether they are an inherited trait, or whether they are some combination of both.

5.4 Conclusion

In conclusion, the results of the three studies presented herein provide important and novel findings regarding the neural correlates of emotional flexibility and how these regions may contribute to psychiatric illnesses, like major depressive disorder. We observed that amygdala reactivity in individuals with depression varied as a function of task-demands, which suggests that negatively-biased emotion processing may not occur at all levels of information processing in MDD. We also found that the dorsal and lateral regions of the prefrontal cortex were recruited by participants with MDD during direct emotion regulation, similar to controls, though they reported significantly less emotion regulation. Consistent with these findings, during the down-regulation of negative emotions controls had reduced activity in the amygdala and perceptual/sensory cortices. Conversely, participants with MDD displayed increased activity in these regions. Finally, we also observed a significant relationship between structural and behavioural correlates of emotional flexibility. Specifically, the pattern of amygdala connectivity significantly predicts individual differences in trait-anxiety. Together, these findings also emphasize the importance of emotion perception in models of psychopathology. In conclusion, recent studies, along with the present research, highlight the potential for combining both functional and structural imaging to provide a richer, more thorough, understanding of the neural correlates of emotional flexibility.

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Research Ethics

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Dr. Derek Mitchell
 File Number: 4702
 Review Level: Delegated
 Approved Local Adult Participants: 290
 Approved Local Minor Participants: 0
 Protocol Title: The neurobiological basis of affective and social dysregulation (REB #13616)
 Department & Institution: Schulich School of Medicine and Dentistry/Psychiatry, London Health Sciences Centre
 Sponsor: Natural Sciences and Engineering Research Council

Ethics Approval Date: September 27, 2012 Expiry Date: August 31, 2014
 Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Revised Western University Protocol	Increase in local sample size to 290	
Revised Letter of Information & Consent	Part A: Patient Volunteers	2012/08/22
Revised Letter of Information & Consent	Part B: Healthy Volunteers	2012/08/22

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The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

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Curriculum Vitae

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Publications:

1. **Greening, SG**, Mitchell, DGV (Submitted) A network of amygdala connections predict individual differences in trait-anxiety.
2. **Greening, SG**, Norton, L, Virani, K, Ty, A, Mitchell, DGV, Finger, EC (Submitted) Individual differences in the anterior insula associated with the likelihood of helping versus harming others.
3. Ruiz Vargas, E, **Greening, SG**, Mitchell, DGV, Wahl, LM (Submitted) Topology of whole-brain fMRI networks: a weighted network analysis.
4. Ruiz Vargas, E, **Greening, SG**, Mitchell, DGV, Wahl, LM (Submitted) Network analysis of human fMRI data suggests modular restructuring after simulating concussion in healthy subjects.
5. Kryklywy, JH, Macpherson, EA, **Greening, SG**, Mitchell, DGV (In Press) Emotion modulates activity in the 'what' but not 'where' auditory processing pathway.
6. **Greening, SG**, Osuch, E, Williamson, PC, Mitchell, DGV (In Press) The neural correlates of regulating positive and negative emotions in medication-free major depression. *Social Cognitive and Affective Neuroscience*.
7. **Greening, SG**, Osuch, E, Williamson, PC, Mitchell, DGV (In Press) Emotion-related brain activity to conflicting socio-emotional cues in unmedicated depression. *Journal of Affective Disorders*.
8. Mitchell, DGV, **Greening, SG** (2012) Conscious perception of emotional stimuli: Brain mechanisms. *The Neuroscientist*. 18(4): 386-398.
9. Han, T, Alders, GL, **Greening, SG**, Neufeld, RWJ, Mitchell, DGV (2012) Do fearful eyes activate empathy-related brain regions in individuals with high psychopathic traits? *Social Cognitive and Affective Neuroscience*. 7(8): 958-68.
10. **Greening, SG**, Finger, EC, Mitchell, DGV (2011) Parsing decision making processes in prefrontal cortex: Response inhibition, overcoming learned avoidance, and reversal learning. *NeuroImage*. 54(2): 1432-41.
11. Amting, JM*, **Greening, SG***, Mitchell, DGV (2010) Multiple mechanisms of consciousness: The neural correlates of emotional awareness. *Journal of Neuroscience*. 30(30): 10039-47.***Co-first authors**
12. Gorczynski, P, Faulkner, G, **Greening, SG**, Cohen, T (2010) Exploring the Construct Validity of the Transtheoretical Model to Structure Physical Activity Interventions for Individuals with Serious Mental Illness. *Psychiatric Rehabilitation Journal*, 34(1): 61-4.