SUBREGIONAL ACTIVATION OF THE AMYGDALA DURING EMOTIONAL MEMORY ENCODING IN POSTTRAUMATIC STRESS DISORDER: AN FMRI INVESTIGATION

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Subregional Activation of the Amygdala during Emotional Memory Encoding in Posttraumatic Stress Disorder: An fMRI Investigation

Doctor of Philosophy, Summer 2014

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Posttraumatic stress disorder (PTSD) is characterized as a debilitating and disruptive psychiatric condition that arises following exposure to a single or multiple traumatic events. The disorder expresses itself as a constellation of physical, cognitive, and emotional symptoms and leads to significant impairment in social and occupation functioning. In Canada, the majority of Canadians are exposed to at least one traumatic event in their lifetime and almost one in ten Canadians go on to develop the disorder. Despite evolving conceptualizations of PTSD, re-experiencing symptoms related to recurrent and intrusive memories remains a core feature of the disorder, and these recollections often accompany other changes in memory. The mechanisms underlying memory disturbances in PTSD however, remain less clear. Early fear conditioning studies in non-human primates implicated alterations to the basolateral subdivision of the amygdala (BLA) in the pathogenesis of PTSD, due to its role in learning and memory for threatening events. The overall goal of this dissertation was to examine whether PTSD is associated with alterations in functional brain activation across three distinct subregions of the amygdala during memory encoding of emotional events varying in valence and arousal. Specifically, using functional magnetic resonance imaging (fMRI) and analysis methods based on probabilistic cytoarchitectonic mapping, activation of the amygdala subregions was examined for a series of photos that participants viewed in the fMRI scanner, and then later remembered during a recognition memory test. Consistent with the study's primary hypothesis, results

revealed that those with PTSD (n = 11) showed greater activation of the BLA during encoding of negative relative to positive photos. This effect was unique to the BLA compared with the centromedial amygdala. No subregional differences emerged in the trauma-exposed control group (n = 11). Moreover, the BLA memory effect in the PTSD group was also observed when comorbid depressive symptoms were statistically controlled, and showed a marginally significant effect toward independently predicting symptom severity. Contrary to the study's hypotheses, there was no evidence of altered BLA activity during memory encoding of high arousing relative to low arousing events. Overall, the results of this dissertation suggest that task-based activation of the amygdala in PTSD is not consistent across the entire structure, and that memory-related processing of negative information is associated with recruitment of the BLA.

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Dedication

Mom and Dad

The many opportunities you have provided me have helped to shape me in every way possible and I am eternally grateful for all that you have done to support me. Thank you for instilling in me the value of a strong work ethic and for teaching me to never give up.

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Chapter 1: Introduction

Unlike many other clinical disorders, the etiology of posttraumatic stress disorder (PTSD) can be circumscribed to a specific event. These events involve exposure to or actual threatened death, serious injury, or sexual violation, and the threshold at which such exposure leads to PTSD arises when a constellation of persisting symptoms results in decreased occupational and social functioning (American Psychiatric Association, 2013). Epidemiological data indicate that the rate of lifetime PTSD in Canada is approximately 9.2%, with a rate of current PTSD (symptoms for 1 month) estimated to be 2.4% (Van Ameringen, Mancini, Patterson, & Boyle, 2008). Effective treatments such as cognitive-behavioural therapy aim to reduce symptoms of posttraumatic stress through gradual exposure and processing of trauma-related cues such as thoughts, feelings, and situations (Debiec, Bush, & LeDoux, 2011). Pharmacological interventions are used either alone or in conjunction with exposure-based therapies (Cukor, Olden, Lee & Diefede, 2010). Despite their relative success, a sizable proportion of individuals with PTSD do not respond to treatment (Resick, Monson, & Gutner, 2007). The basic pathophysiology of PTSD is still poorly understood and elucidating its neurobiological underpinnings has been identified as a critical step toward advancing treatment of this disorder (Garfinkel & Liberzon, 2009).

Intrusive trauma recollections and memory disturbances are a hallmark feature of PTSD. Early functional neuroimaging findings implicated amygdala hyperactivity as the neurobiological substrate underlying trauma-based memories. Based on evidence that revealed changes in both structure and function, this brain structure was readily incorporated in traditional neurocircuitry models of PTSD (Rauch, Shin, & Phelps; 2006; Rauch, Shin, Whalen, & Pitman,1998). However, as the number of separate investigations grew, variability with respect to hyperactive amygdala function was observed, suggesting that altered functioning may only

occur under selective conditions. Although neuroimaging investigations of PTSD in humans were underway, animal models of fear learning and memory had already established that the amygdala was not a unitary structure and that its subdivisions played distinct roles in mediating behaviour. More recently, with advanced neuroimaging tools for analysis, brain-behaviour investigations of amygdala subregions in humans have garnered more attention (e.g., Boll, Gamer, Gluth, Finsterbusch, & Büchel, 2013; Etkin, Prater, Schatzberg, Menon, & Greicius, 2009).

Main Objectives

The overall goal of this dissertation was to use functional magnetic resonance imaging (fMRI) to examine activation across three separate amygdala subregions during emotional memory encoding in PTSD. Specifically, analysis methods based on cytoarchitectonic probabilistic mapping to define three separate amygdala subregions were undertaken. Using these methods I extracted the mean activation across each of the amygdala subregions when participants encoded a series of emotional photos varying in valence and arousal.

The next chapter begins with an overview of current pathophysiological models of PTSD. Following this, I introduce relevant findings from animal fear conditioning experiments. Next, an extensive review of the literature is presented that covers both behavioural and neuroimaging research on emotion and memory, in both healthy individuals and in those affected by PTSD. I then review the available functional neuroimaging research on amygdala subregions in humans and discuss how this relates to the study of PTSD. Last, I outline the primary objectives and my corresponding hypotheses for the current study.

Chapter 2: Literature Review

2.1.0 Pathophysiological Models of PTSD

Over the last few decades, several pathophysiological models of PTSD have been put forward. These models attempt to provide a framework for understanding symptoms from the perspective of brain structure and function. The traditional neurocircuitry model first proposed by Rauch and colleagues (1998) related symptoms of PTSD to dysfunction in a core of set of brain regions. Specifically, the model proposes that deficits in attention or awareness, including the inability to suppress attention to trauma-related stimuli, is related to decreased recruitment of the medial prefrontal cortex. The model further posits that decreased engagement of the medial prefrontal cortex results in a loss of top-down control over areas of the limbic system, and as a consequence, exaggerated amygdala activity underlies the vivid and intrusive nature of trauma recollections and mediates symptoms of hyperarousal. Changes to the neighbouring hippocampus underlie additional learning and memory deficits, including the generalization of threat to non-threatening situations (i.e., abnormal extinction processes; Rauch et al., 2000).

Other models less focused on threat have proposed that dysfunction in the cortical midline structures, such as the medial prefrontal cortex, along with the amygdala, insula, posterior parietal cortex and temporal poles, underlie changes in self-referential and social cognitive processes, and that these deficits may account for symptoms of negative self-appraisals and emotional numbing (Lanius, Bluhm, & Frewen, 2011). Although this model aims to characterize more complex forms of PTSD (i.e., repeated trauma exposure during critical periods of development), various symptoms of emotion dysregulation are often observed across PTSD subtypes. As in the traditional neurocircuitry model, dysfunction in prefrontal-amygdala pathways is also implicated, but greater emphasis is placed on dysregulation of emotions beyond

fear. The model emphasizes two main processes of emotional dysregulation: 1) *undermodulation* of affect, which is characterized by trauma re-experiencing and symptoms of hyperarousal, and mediated by a lack of top-down prefrontal inhibition resulting in increased amygdala activation; and 2) *overmodulation*, which occurs when an individual distances or dissociates from an emotional experience, thus leading to symptoms of depersonalization, derealization and emotional numbing. This form of emotion modulation is characterized by increased top-down prefrontal inhibition, thus resulting in decreased amygdala activation (Lanius et al., 2010b; 2011).

In their model, Paulus and Stein (2006) emphasize abnormal autonomic processes as central to the expression of anxiety-like symptoms in PTSD. The authors propose that individuals who are prone to experience an interoceptive state as dangerous have an augmented signal between their observed and expected body state. Both cognitive (e.g., worrying) and behavioural (e.g., avoidance) symptoms arise from neural resources attempting to attenuate the discrepancy between these two states (Paulus & Stein, 2006). Heightened interoceptive signals are thought to be mediated by hyperactivity in the anterior insula. Through its extensive bidirectional connections with the amygdala, the amygdala is thought to process and then relay information regarding the relative saliency of a stimulus (appetitive or aversive) to the insula.

Although different clinical aspects and their underlying neurobiology are emphasized across these models, each model implicates altered functioning of the amygdala as a critical neurobiological marker of PTSD. Changes in amygdala function have been related to disturbance in a number of functions, including trauma and non-trauma memory, emotion regulation, and saliency processing. The convergence of these models on altered amygdala function warrants a more in-depth investigation of how the amygdala's unique functional properties may relate to the

expression of PTSD symptoms. This dissertation aims to undertake such an investigation and specifically focuses on amygdala functioning and its relation to memory for emotional information in PTSD.

2.2.0 Animal Models of Fear: Relevant Findings

Animal models of fear learning and memory have provided a valuable framework for investigating the neurobiological underpinnings of PTSD, because many symptoms of PTSD, including those related to trauma re-experiencing and avoidance of trauma-related cues, are intrinsically linked to memory-related mechanisms (Glover et al., 2011). Endogenous stress-related hormones such as norepinephrine have been implicated in both normal and pathological fear and anxiety, and play an important role in memory consolidation (Debiec et al., 2011). In rodents, a body of work has shown that post-training administration of adrenal stress hormones can enhance fear conditioning, i.e., the expression of fear behaviours such as freezing or avoidance (McGaugh, Cahill, & Roozendaal, 1996). These animal fear-based paradigms are used to model stress and memory processes thought to occur in humans. Early animal studies using electrical stimulation methods first pointed to the amygdala, a small brain region situated in the medial temporal lobe, as a site that modulates the effects of stress hormones on memory (Goddard, 1964; Gold & van Buskirk, 1978; McDonough & Kesner, 1971; as reviewed in Gold & McGaugh, 1975). Later lesion studies confirmed that the amygdala was directly involved in memory modulation via stress hormones. Inactivation of the amygdala using post-training infusions of β-adrenergic antagonists (e.g., propranolol) was shown to block the memory enhancing effects of norepinephrine (Liang, Juler, & McGaugh, 1986).

Important later animal studies revealed that the amygdala's role in modulating memory was not a function of the entire structure, but instead, localized to one of its subregions, the

basolateral nucleus (basolateral amygdala, BLA). Administration of a glucocorticoid agonist into the BLA, but not centromedial amygdala (CMA), produced dose-dependent enhanced retention in an inhibitory avoidance task, i.e., increased latency to enter a compartment previously paired with a shock (Roozendaal & McGaugh, 1997). Conversely, pre-training infusion of a glucocorticoid antagonist into the BLA, and not the CMA, impaired retention in a water maze escape task, i.e., increased latency to find escape platform (Roozendaal & McGaugh, 1997). Further work demonstrated that administration of a β-adrenoceptor antagonist into the BLA blocks the memory enhancing effects of systemically administered corticosterone (Roozendaal et al., 2006) and protects against the memory-impairing effects induced by adrenalectomy (Roozendaal, Portillo-Marquez, & McGaugh, 1996).

Taken together, these findings indicate that the BLA acts as the neural substrate by which memory for aversive events is either enhanced or impaired relative to neutral events. Importantly, lesions to the BLA also block the memory-enhancing effects of the glucocorticoid agonists administered directly into the hippocampus (Roozendaal & McGaugh, 1997, Roozendaal, Nguyen, Power, & McGaugh, 1999). These latter findings underscore the critical role of the BLA in regulating memory consolidation via its interactions with other brain regions (Roozendal & McGaugh, 2011). Further understanding of the BLA's role in relation to emotion and memory in humans may therefore have important implications for understanding the basic pathophysiology of PTSD.

2.3.0 The Cognitive Neuroscience of Emotional Memory

Converging lines of evidence have confirmed that the amygdala is involved in mediating emotional memories in humans. Both anecdotal and laboratory evidence demonstrate that emotionally salient events are better remembered than more mundane events, a phenomenon

often referred to as the "emotional enhancement of memory" or more simply, "emotional memory." Humans with selective bilateral amygdala damage fail to show the normal emotional enhancement of memory, relative to both normal and brain-damaged controls (Adolphs, Cahill, Schul, & Babinksy, 1997). Studies involving patients with unilateral lesions to the temporal lobe have also confirmed that damage to the amygdala is associated with failure to produce the normal memory enhancement for emotional information (e.g., Frank & Tomaz, 2003; Labar & Phelps, 1998). Despite amygdala damage, these patients show both intact physiological (LaBar & Phelps, 1998) and subjective (Adolphs et al., 1997) responses to emotion, thus supporting the idea that the amygdala modulates the effects of stress hormones on memory for emotional events.

Studies employing functional neuroimaging methods in healthy individuals have provided further evidence that the influence of emotion on memory involves the amygdala. Using positron emission tomography, Cahill et al. (1996) demonstrated that amygdala activity during the presentation of emotional film clips, was highly correlated with later recall of emotional versus neutral film clips. Also using positron emission tomography, Hamman, Eli, Grafton, and Kilts (1999) found that bilateral amygdala activation during encoding of both negative and positive scenes significantly correlated with their subsequent recognition memory, which was enhanced relative to neutral scenes.

Studies using fMRI have yielded similar results. Using provocative scene stimuli, Canli, Zhao, Brewer, Gabrieli, and Cahill (2000) found that higher ratings of individually experienced emotional intensity were associated with bilateral amygdala activity, and that amygdala activity was predictive of subsequent memory only for those scenes that were rated as the most emotionally intense. Similar effects have also been observed after delay periods of up to one year

(Dolcos, LaBar, & Cabeza, 2005). These findings in humans are highly consistent with animal studies demonstrating that recruitment of the amygdala is critically involved in the expression of enhanced memory for emotional events.

Also in line with findings from the animal literature, the human amgydala appears to mediate the emotional memory effect through its interactions with other brain regions. For instance, in an fMRI study by Kensinger and Corkin (2004), hippocampal activation was related to successful memory performance for both negatively arousing and negative nonarousing word stimuli (i.e., the amount of hippocampal activity at study predicted whether the words would later be remembered or forgotten). Amygdala activity also predicted successful memory performance, but only for the arousing words. Critically, there was a positive correlation between activation of the amygdala and the hippocampus during the encoding of arousing words. These results provide evidence of an interaction between amygdala and hippocampal activation, and subsequent memory for emotionally arousing items (Kensinger, 2004).

fMRI findings also reveal that brain regions involved in emotional memory are differentially engaged by various stimulus properties, including valence and arousal. According to the circumplex model of affect (Posner, Russell & Peterson, 2005; Russell, 1980), emotions are represented by different combinations of these two continuous dimensions. Whereas valence refers to the quality of the emotion and is measured on a continuum ranging from positive to negative, arousal refers to the intensity of the emotion and is measured on a continuum ranging from high to low. Mickley Steinmetz and Kensinger (2009) found that, whereas temporal lobe activity was the strongest predictor of later memory for high arousing and negative photos, frontal activity was the strongest predictor of low arousing and positive photos. The authors suggest that temporal-occipital activity during encoding of negatively arousing items may reflect

enhanced sensory processing, whereas the frontal activity during the encoding of positive items may reflect a greater degree of elaborative semantic processing, because positive items are processed in a more conceptual and heuristic fashion than negative items (Fredrickson & Branigan, 2005; Rowe, Hirsh, & Anderson, 2007). These findings indicate that, in addition to having additive or interactive effects, valence and arousal may also have separable or independent effects on the expression of emotional memory and its underlying neural networks.

In summary, humans exhibit a memory advantage for emotional events over more mundane events. Amygdala activation during encoding of emotional stimuli can predict whether these events are later successfully remembered. The consolidation of emotional events into memory appears to further depend on the interactions between a set of functionally inter-connected regions including the amygdala, hippocampus, and the prefrontal cortex, where each are differentially engaged by unique stimulus properties such as arousal and valence. It is only recently that more fined-grained analyses regarding the roles of amygdala subregions are being investigated in humans, as discussed further below. The next section reviews the broader focus on the study of emotional memory in PTSD and specific evidence for the presence of amygdala dysfunction.

2.3.1 Emotional Memory in PTSD: Evidence for Amygdala Dysfunction

Although a number of cognitive impairments have been documented in PTSD, including deficits related to attention/inhibition (Falconer et al., 2008), working memory (Morey et al., 2009; Weber et al., 2005), and conflict monitoring (e.g., Stroop; Shin et al., 2001), dysfunction in memory is core to both the onset and maintenance of the disorder (Ehlers & Clark, 2000). Recent meta-analytic findings demonstrate PTSD is reliably associated with decreased memory performance for both visual and verbal information (Brewen, Kleiner, Vasterling, & Field,

2007). However, these findings are based on studies that examined memory performance for information void of emotional content. Examining memory for emotion-laden information may be more relevant from an ecological standpoint to PTSD, given the emotional intensity that is typically associated with traumatic events (Talarico & Rubin, 2003).

Neuroimaging studies of emotional memory in PTSD have yielded interesting results. Using fMRI, Dickie, Brunet, Akerib, and Armony (2008), examined functional brain changes involved in memory encoding of fearful and neutral faces in a group of PTSD participants. Participants were first shown a series of fearful and neutral faces while they underwent an fMRI scan, after which they completed a recognition memory task where they were required to indicate the faces they had not seen before (i.e., "new" faces) versus faces that were previously presented during scanning session (i.e., "old" faces). The authors found that overall memory performance, indexed by hit rate minus false alarm rate, was negatively correlated with PTSD symptoms measured with the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995). That is, increasing PTSD symptom severity was related to reduced face recognition performance, irrespective of emotion type. Importantly, in contrast to other regions (i.e., hippocampus and ventromedial prefrontal cortex), only amygdala activity at encoding predicted memory performance for the fearful faces. This activity was also positively correlated with symptom severity.

In a follow-up longitudinal study (Dickie, Brunet, Akerib, & Armony, 2011), the same group of PTSD patients underwent a second fMRI scanning session (i.e., "time 2"), and at which point their symptoms had decreased by approximately 50% relative to the first scan (i.e., "time 1"). Similar to time 1, the authors found that greater amygdala activity positively correlated with memory performance for fearful faces that were subsequently remembered, in addition to greater

symptom severity. In contrast, recognition of neutral faces was associated with decreasing amygdala activity, as a function of symptom severity. In other words, greater symptom severity predicted lower amygdala activity during successful encoding of neutral faces.

These results demonstrate that across time, PTSD symptom severity is positively associated with greater amygdala activity during encoding of negative or threatening events that are later remembered, and this appears to come at the cost of decreasing activation toward neutral information. These results further corroborate that emotional memory-related activity in the amydala may play a significant role in the maintenance of PTSD symptoms. However, in the absence of any control group, findings reported by Dickie and colleagues make it difficult to draw any firm conclusions.

Using a control group without a history of trauma-exposure, Thomaes et al. (2009) failed to find any amygdala activation during deep encoding of negative words that were later remembered. Instead, the authors found PTSD was associated with greater activation of the hippocampus, extending into the parahippocampal and fusiform gyrus, during deep encoding of negative words relative to baseline. In contrast, Hayes et al. (2011) reported that relative to a control group with a history of trauma-exposure, those with PTSD showed reduced activity in the amygdala during encoding of trauma-related photos that were subsequently remembered versus forgotten.

The findings reported in the above studies offer different views of amygdala function and its relation to emotional memory in PTSD. The amygdala appears to be over-recruited under some conditions, under-recruited in other instances, and in some cases, may even have no relation. This inconsistency across studies may be attributed to heterogeneity across a number of study dimensions, including the nature of the probing stimuli and their actual relation to the

trauma. Symptom provocation studies offer unique insights into the nature of amygdala function both in terms of trauma specificity and emotional recollection. In these studies, participants prepare written or audio descriptions of both neutral and traumatic autobiographical events ahead of scanning. During scanning, these scripts are playbacked to evoke imagery and sensory-related experiences (olfactory, auditory, somatosensory) of the autobiographical event (Lanius et al., 2001; Shin et al., 1997). Using this symptom provocation paradigm, Lanius et al. (2001) found that, as compared with a trauma-exposed control group, those with PTSD showed less activation in a number of regions including frontal regions (anterior cingulate and medial prefrontal gyrus) and the thalamus. However, at no point was amygdala activation observed during recall of the traumatic memory, in either group. A lack of amygdala activation has also been observed in other similar provocation studies (Bremner et al., 1999; Lanius et al., 2002, 2003, 2004, 2005). On the basis of these and other similar findings, some have proposed that hyperactive amygdala in PTSD is more readily observed under conditions of generalized threat as opposed to trauma-specific events (Rauch et al., 2000). Consequently, this would correspond to a constellation of symptoms that are often not trauma-specific in PTSD. This notion is supported by neuroimaging studies that have found exaggerated amygdala activity in PTSD in response to fear or threat-based stimuli that are not trauma-related (Armony, Corbo, Clement, & Brunet, 2005; Rauch et al., 2000; Shin et al., 2005).

In summary, PTSD is associated with altered functioning of neural systems associated with emotional memory, and although some studies have found altered activation of the amygdala, others have not. Inconsistent findings may be in part due to heterogeneity among a number of study variables including use of a control group, type of control group (history of trauma exposure versus non-trauma exposure; see meta-analysis by Patel, Spreng, Shin, &

Girard, 2012), the nature of experimental stimuli and their degree of relatedness to trauma etiology. Although all of these variables have been raised as sources of variation in the literature, little attention has been given to the composition of the amygdala, because the vast majority of studies have treated this structure as a single, homogeneous structure. The amygdala and its subregions likely make distinct contributions from a functional perspective, and treating it as a unitary structure may mask subregion-specific effects, leading to some of the observed variability across studies. The next section more closely reviews evidence regarding amygdala subregions and their relation to PTSD.

2.4.0 Elucidating the Role of Amygdala Subregions in PTSD

As reviewed above, a large body of animal studies demonstrates that the amygdala is not a unitary structure and is composed of a complex of structurally and functionally heterogenous nuclei (Whalen & Phelps, 2009). Rodent studies show that the BLA in particular, plays a specialized role in mediating the retention of defensive fear behaviours. In humans, three major subdivisions of the amygdala include the BLA, which consists of the lateral, basolateral, basomedial, and basoventral nuclei, the CMA, which is composed of the central and medial nuclei, and the superficial subdivision (SFA), which lies adjacent to the basolateral subdivision and includes the cortical nuclei (Roy et al., 2009; see Figures 1 and 2).

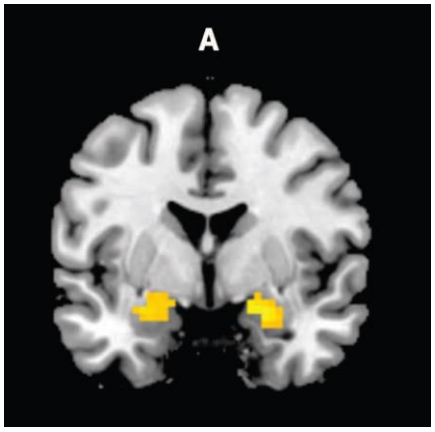

Figure 1. Coronal view (top and bottom of the figure correspond respectively to the top and bottom of the brain) of amygdala activation (via fMRI) in the context of the whole brain, in a group of healthy participants reported by Agren et al. 2012; Figure 2A reproduced with permission from publisher.

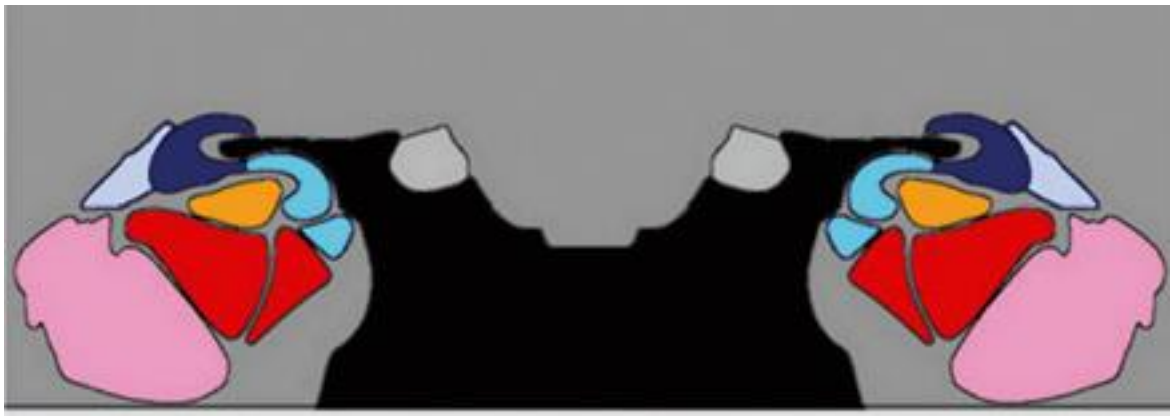

Figure 2. Schematic drawing of amygdala subregions in coronal view: the lateral (pink) and basolateral nuclei (red) make up the *basolateral subregion (BLA)*; the central (light blue) and medial (dark blue/purple) nuclei make up the *centromedial subregion (CMA)* and the cortical (turquoise blue) and accessory basal (orange) nuclei make up the *superficial subdivision* (SFA), as reported by Boll et al., 2013; Figure 5A reproduced with permission from publisher.

Significant advances have been made to reliably identify these subregions of the human amygdala. Using post-mortem brains, Amunts et al. (2005) delineated probabilistic maps of human amygdala subregions using cytoarchitectonic mapping methods. Functional neuroimaging studies have begun to apply these mapping methods to further understand the underlying functions of the human amygdala subdivisions. For instance, in healthy individuals, Ball et al. (2007) found that the BLA showed increased activation as indexed by the blood-oxygen-level dependent (BOLD) response to both pleasant and unpleasant auditory melodies, while both the CMA and SFA subdivisions showed a decrease in the BOLD signal. These findings are largely consistent with animal studies that show the BLA receives many afferent inputs from sensory regions. In 2009, Goossens and colleagues found that the SFA selectively responds to facial expressions (i.e., fearful, happy, neutral) in contrast to photos of houses, indicating that this subregion may play a specialized role in the processing of social and affective information.

Using resting-state functional connectivity analyses (used to assess correlated activity among multiple regions at rest), Etkin et al. (2009) found robust connectivity between the BLA and the entire occipital lobe and large parts of the temporal lobe in healthy controls. These targets represent primary and higher-order association cortices for the visual and auditory systems, respectively. There was also strong connectivity of the BLA to areas of the medial prefrontal cortex and parahippocampal gyrus. In contrast, the CMA was associated with strong connectivity to subcortical structures, including the thalamus, midbrain, medulla, cerebellum, and caudate nucleus. Furthermore, Etkin et al. (2009) found alterations in connectivity within amygdalar subregions, and to other regions, in patients with generalized anxiety disorder. This

finding was in part due to lower connectivity of the BLA and the CMA to all of their targets and increased connectivity to their neighbouring subregions' targets.

These functional connectivity data, together with emerging evidence from functional neuroimaging studies, suggest that subregions of the human amygdala likely have discrete and specialized functions. Moreover, the functional correlates of these subregions are likely to be compromised in clinical populations, including those with PTSD. Evidence to support this notion comes from Onur et al. (2009), who found that administration of reboxetine, a norepinephrine reuptake inhibitor, two hours prior to an fMRI scanning session in healthy adults, induced an amygdala response bias toward fear signals that did not exist at baseline in the placebo group. Specifically, reboxetine administration led to enhanced activity of the right BLA in response to fearful stimuli and decreased activation to neutral stimuli.

Onur and colleagues' (2009) findings are similar to those found by Dickie et al. (2011) in a group of individuals with PTSD, but in the absence of any subregional specificity. On the basis of their findings, Onur et al. (2009) proposed that stress-induced increases in norepinephrine signaling may result in converting a subset of BLA neurons into a "fear module" by increasing their sensitivity (i.e., augmenting the signal to noise ratio) toward fearful information at the cost of neutral information. Given that traumatic events are typically associated with an increase in NE signaling, Onur et al. (2009) propose that disinhibited norepinephrine signaling could serve as a crucial etiological contributor to the onset and maintenance of PTSD by eliciting exaggerated BLA responses to the trauma-related cues. The findings by Onur et al. (2009) also parallel findings reviewed earlier that demonstrate a selective involvement of BLA in mediating fear-based learning and memory processes in rodents. However, the link between increased sensitivity of BLA neurons and memory has not yet been established. Specifically, it is currently

unknown whether the BLA, in contrast to the other subregions (CMA, SFA), shows a selective effect of heightened activity for emotional events that are later remembered.

Chapter 3: Primary Objectives and Hypotheses

The primary aim of the current study is to use fMRI to investigate whether PTSD is associated with greater activity in the BLA during successful encoding of emotional events, as compared with a trauma-exposed but no PTSD control (TEC) group. Further unknown is whether this hypothesized effect of increased activity is specific to the BLA versus the other amygdala subregions. On the basis of the findings reviewed here, I hypothesized that, relative to the TEC group, those with PTSD would show greater BLA activity during successful encoding of emotional events, but this effect would not extend to the other amygdala subregions.

Further, because it remains unclear as to what conditions the amygdala may be over-recruited in PTSD, the current study also aims to investigate whether emotional valence and arousal have independent effects on subregional amygdala function. Specifically, it is hypothesized, that relative to the TEC group, those with PTSD will show greater BLA activity during encoding of negative relative to positive events, and during high arousing relative to low arousing events. These hypotheses are supported by a body of studies that suggest that while the amygdala is involved in processing a range of emotional information, it is most sensitive to negative and high arousing information. Moreover, these two specific emotional properties appear to be most relevant to the etiological and clinical manifestations of trauma exposure in PTSD.

Chapter 4: Method

Participants

A total of 22 participants were recruited into one of two groups: those with a current diagnosis of PTSD (*n* = 11) and those who had experienced a traumatic event but who were never diagnosed with PTSD secondary to their traumatic event (TEC group*; n* = 11). All recruitment and testing procedures were approved by the ethics review boards of Ryerson University and the University Hospital Network (Toronto, ON). All participants were assessed for PTSD using the CAPS (Blake et al., 1995), which was administered and scored by graduate trainees under the supervision of two clinical psychologists, N.P-M. and C.M.

Inclusion criteria for the PTSD group were a CAPS score greater than 45 and the presence of at least one re-experiencing symptom, three numbing or avoidance symptoms, and two hyperarousal symptoms. In the current study, for an item in the CAPS to meet diagnostic threshold an individual had to receive a score of at least 1 on frequency and a 2 on intensity, and ratings were made for the past month. Additionally, participants did not have any history of neurological, learning, or psychotic disorders. The PTSD group had a mean CAPS score of 70.09 (*SD* = 14.24; see Table 1) and the nature of trauma exposure for these participants included physical assault and/or death threats (*n* = 4), sexual assault (*n* = 5), witnessing a violent physical assault or death (*n* = 1), and combat exposure (*n* = 1). Psychological comorbidity was assessed through structured psychodiagnostic assessment. The majority of participants (*n* = 19) were assessed with the Mini International Neuropsychiatric Interview (Lecrubier et al., 1997), with the exception of three participants who were assessed with the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, &Williams, 2002a, 2002b.) This difference in clinician-administered assessment of comorbid diagnoses reflected differences in study protocols from

which the current study recruited participants. In the PTSD group, three participants were free of comorbid diagnoses, while the remaining eight presented with one or more comorbid disorders, including major depression (n = 4), anxiety disorder (n = 6), and substance abuse/dependence (n = 2). In terms of medication, six participants were not taking psychotropic medications at the time of testing, while the remaining five were taking prescribed antidepressant medication (these included bupropion, venlafaxine, sertraline, and/or trazadone).

Eleven trauma-exposed participants without a PTSD diagnosis (TEC group) were recruited as a control group. Inclusion criteria for the TEC group required individuals to have experienced a traumatic event (as assessed by criterion A of the CAPS) and have a total CAPS score of less than 30. The nature of trauma for these participants included motor vehicle or biking accident (n = 5), physical assault and/or death threats (n = 2), and witnessing a violent physical assault or death (n = 4). The majority of participants were free of any comorbid diagnosis (n = 9), while the remaining participants presented with a comorbid anxiety disorder (n = 2). In terms of medication, nine participants in the TEC group were not taking psychotropic medications at the time of testing. One of the remaining two participants was taking prescribed antidepressant medication (venlafaxine), whereas the other participant was taking non-psychotropic medication (prednisone, azathioprine, and sulfadiazine). Across both groups, an independent samples t-test revealed a marginally significant finding that those participants taking medication had higher average CAPS scores (M = 58.14, SD = 34.60) than those not taking medication (M = 34.20, SD = 27.69), $t(20) = -1.75$, $p = .096$, $g = 0.73$

The TEC group did not differ from the PTSD group with respect to age, education, or sex (Table 1). In terms of time elapsed since trauma, the TEC group ranged between 4 and 24 months (M = 10.27, SD = 6.02; Mdn = 10.00), whereas the PTSD group ranged between 3 and

372 months (*M* = 74.32, *SD* = 116.84; *Mdn* = 12.00). In the latter group, three participants had experienced their traumatic event greater than 15 years ago.[1] Depressive symptoms were assessed using the Beck Depression Inventory-II (BDI-II; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; Table 1). BDI-II scores significantly correlated with CAPS scores ($r = 0.62$, $p = .002$). Given their relation to group status, the main analyses were repeated with BDI-II scores and medication as covariate variables, in order to assess their relation to the findings. There was no correlation between BDI-II scores and medication use ($r = 0.15$, $p = .662$).

Table 1. Demographic and Clinical Information of Participants

Group	Trauma-Exposed Controls (n = 11)	PTSD (n = 11)
Age (Years)	31.45 (10.72)	34.46 (13.59)
Sex[a] (m/f)	3/8	5/6
Education	14.36 (2.24)	13.90 (2.47)
CAPS**	13.54 (10.20)	70.09 (14.24)
BDI-II*	6.00 (8.31)	18.90 (12.48)

Data shown: Mean (SD)

CAPS: Clinical Administered PTSD Scale; BDI-II: Beck-Depression Inventory-II

[a] A chi square analysis did not reveal any statistically significant gender differences between groups; p =.375

*p <.01; **p <.001 (statistical difference between groups, corrected for multiple comparisions using Bonferonni method)

Materials

The stimuli used in the current experiment have been described elsewhere (Mickley Steinmetz & Kensinger, 2009). Briefly, a total of 350 photos were selected from the International Affective Picture System database (IAPS; Lang, Bradley, & Cuthbert, 1997; also see Appendix VIII for a set of sample images). The entire set consists of 70 negative arousing (*M* valence =

[1] Although best efforts were made to match the two groups on any many dimensions as possible including time since trauma, varying rates of recruitment and high number of individuals meeting exclusion criteria were among two main factors that made this endeavour challenging. A more detailed account of how groups' composition may have affected the observed results is presented in the Discussion section.

2.9, *SD* = 0.76; *M* arousal = 5.9, *SD* = 0.48), 70 negative nonarousing (*M* valence = 2.9, *SD* = 0.71; *M* arousal = 4.2, *SD* = 0.66), 70 positive arousing (*M* valence = 7.2, SD = 0.54; *M* arousal = 5.9, *SD* = 0.57), 70 positive nonarousing (*M* valence = 7.1, SD = 0.54; *M* arousal = 4.2, *SD* = 0.43), and 70 neutral photos (*M* valence = 5.1, *SD* = 0.38; *M* arousal = 3.3, *SD* = 0.84). Positive, negative, and neutral photos were matched on various dimensions including visual complexity and brightness based on Adobe Photoshop (Adobe Systems, San Jose, CA). Photos in each category were also equated for semantic category by assigning roughly equal numbers of photos from different semantic categories (e.g., people, animals, buildings/landscapes) using normative data from Kensinger and Schacter (2006). The selection of negative photos was not based on participants' individual trauma histories but varied in terms of content (e.g., mutilated bodies, war-combat scenes, acts of violence, weapons), and thus were considered non-trauma specific for the purpose of this dissertation. Using the IAPS normative ratings, both valence and arousal dimensions were equated such that positive and negative photos were equated on arousal level (i.e., positive arousing photos were just as arousing as negative arousing images, and positive nonarousing and negative nonarousing photos were of similarly low arousal levels; p >.200). Arousal was also equated across the valence dimension (e.g., positive arousing photos and positive nonarousing photos were rated as similarly positive in valence, p > .200); the absolute valence differences between the positive and negative stimuli (e.g., the negative and positive photos are given valence ratings that are equivalently far away from neutral valence; p > .200) were also not significantly different.

Procedure

The current experimental procedure was adopted from Mickley Steinmetz and Kensinger (2009). Participants first underwent an fMRI scan while they viewed 175 photos (i.e., 35 from

each emotion category). Each photo stimulus was presented for a total duration of 4000 ms. During this time, participants were asked to make a judgment about the quality of the photo. They were instructed to select "high" when they believed the photo was of "high enough quality to be found in a magazine such as National Geographic or The Smithsonian." In contrast, they were asked to select "low" when they believed the photo to be "not of high enough quality to be found in such a magazine." This task was chosen to ensure participants fully attended to every photo and to minimize the degree to which participants processed the affective content of each photo. Such implicit or "indirect" forms of emotional processing have been associated with greater amygdala activation relative to more explicit or "direct" forms of emotional processing (e.g., Critchley et al., 2000; Hariri, Bookheimer, & Mazziotta, 2000; Keightley et al., 2003). In addition, indirect versus direct forms of emotional encoding have been associated with producing a more robust memory enhancement effect (Patel, Girard, & Green, 2012). Interstimulus intervals ranged between 2 to 14 s, in order to optimize the ability to isolate the hemodynamic response associated with each photo's presentation (Dale, 1999). Approximately 15 minutes later, outside the scanner, participants underwent a surprise recognition test.

In the recognition test, participants were presented with a total of 350 photos, one fifth from each of the 5 emotion categories (i.e., positive arousing, positive nonarousing, negative arousing, negative nonarousing, and neutral). Half of the items from each emotion category were "old" and half were "new". For every photo, participants were asked to respond "old" when they recognized the photo from the encoding/scanning phase, or "new" when they had no memory of ever having seen the photo. Four list sets were created and counterbalanced across participants (e.g., if participant A received List 1 at encoding and List 2 as recognition foils, then participant B received List 2 at encoding and List 1 as recognition foils). Studied items versus nonstudied

foils were balanced for their valence and arousal ratings as well as for brightness and for the number of photos that included people, animals, and buildings/landscapes.

Following the recognition test, participants viewed all 350 photos and rated each one on the two dimensions of valence and arousal. Using the Self-Assessment Manikin (Lang et al., 1997; Appendix IX) participants rated each photo along two separate 5-point, visual analog scales: For the valence dimension, the SAM depicts a graphic character displaying a very unhappy facial expression (*1 = very unpleasant or negative*) to a very happy facial expression (*5 = very pleasant or positive*); the middle character displays a neutral expression (*3 = neutral*). For the arousal dimension, the SAM depicts a graphic character that ranges from sleepy with closed eyes (*1 = Not arousing at all*) to excited with open eyes (*5 = Very arousing*).

fMRI Data Acquisition and Image Preprocessing

Anatomical and functional data were acquired on a 3-T Sigma MR System (GE Medical Systems, Milwaukee). Anatomical scans, for co-registration of functional data, were acquired first using a fast spoiled gradient echo (FSPGR) sequence (**T**$_1$-weighted sequence, 176 slices, FOV = 256 mm, slice thickness = 1 mm, 0 gap, 256 × 256 matrix, resulting in a voxel size of 1.0 × 1.0 × 1.0 mm^3). The functional data were acquired in an interleaved order (EPI, TR = 2.65 s; TE =2.50s; flip angle = 90^o; 39 slices to cover the whole brain, FOV = 192 mm, slice thickness =3.00 mm, 0 gap, 64 × 64 matrix, resulting in a voxel size of 3.0 × 3.0 × 3.0 mm^3). Both anatomical and functional photos were taken in the same axial orientation. In total, there were 3 functional sessions with 142 frames each. The first 4 frames were dropped for signal equilibrium.

Preprocessing and data analyses were completed using SPM8 (Statistical Parametric Mapping, 8; Wellcome Department of Imaging Neuroscience, London, UK). Slice time correction was completed and motion correction was run using a six parameter, rigid body

transformation algorithm by SPM8. Functional photos were co-registered and realigned to the subject's anatomical image. Each participant's anatomical image was segmented by tissue class and spatially normalized to the $\mathbf{T}_1$-weighted Montreal Neurological Institute template (resampling at 2-mm isotropic resolution) and the normalization parameters derived from segmentation of the grey matter were then written to the functional data. fMRI data were then smoothed using a Gaussian kernel of 6 mm full-width half-maximum. SPM motion parameters were inspected for outliers (motion > 2 mm in any direction) but no participants had to be excluded from the analysis.

fMRI Region of Interest (ROI) Analyses

Given the current study's primary questions concern the amygdala, I examined activity among the three amygdala subregions (i.e., basolateral, centromedial, and superficial subdivisions) with the same regional definitions as outlined in Ball et al. (2007). Specifically, the spatial extent of each of these three subregions was determined using stereotaxic, probabilistic maps of cytoarchitectonic boundaries developed by Amunts et al. (2005; Figure 3). The BLA (Left: 1840 mm^3, Right: 1920 mm^3) includes the lateral, basolateral, basomedial, and paralaminar nuclei. The CMA (Left: 176 mm^3, Right: 224 mm^3) consists of the central and medial nuclei. The SFA (Left: 952 mm^3, Right: 760 mm^3) includes the anterior amygdaloid area, the amygdalopyriform transition area, the amygdaloid-hippocampal area and the ventral and posterior cortical nuclei (Roy et al., 2009)[2]. These probabilistic cytoarchitectonic maps were applied to the current fMRI data using SPM Anatomy Toolbox version 1.7 (Eickhoff et al., 2005). This approach derives the mean signal across all voxels falling within each particular subregion.

[2] Inclusion of multiple nuclei within each subdivision is due to the spatial resolution constraints of magnetic resonance imaging.

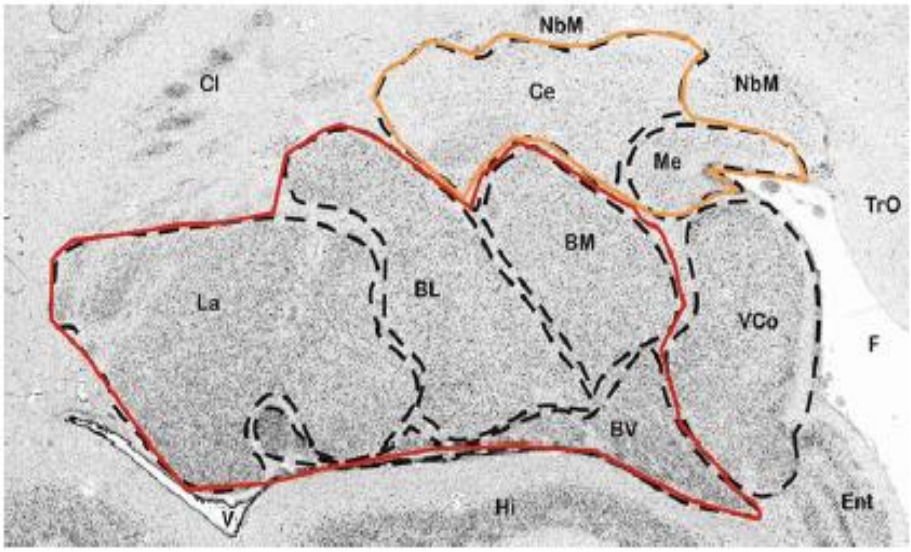

Fig. 1 Cytoarchitecture of the amygdala and neighboring cortical and subcortical structures in a coronal section of a human postmortem brain. The centromedial nucleus is labelled by an *orange line* and the basolateral complex by a *red line*. The *VCo* belongs to the superficially located part of the amygdala. *BL* basolateral nucleus, *BM* basomedial nucleus, *BV* basoventral nucleus, *Ce* central nucleus, *La* lateral nucleus, *Me* medial nucleus, *VCo* (ventral) cortical nucleus. Neighbouring structures: *Cl* Claustrum, *Ent* entorhinal cortex, *F* endorhinal sulcus, *Hi* hippocampus, *NbM* Nucleus basalis of Meynert, *TrO* Tractus opticus, *V* lateral ventricle

Figure 3. Representation of the cytoarchitectonic subregional boundaries of the human amygdala as outlined by Amunts et al. 2005; Figure 1 reproduced with permission from publisher.

Data Analysis

All data were analyzed according to both valence and arousal dimensions. Using IAPS normative data, I categorized stimuli along valence (i.e., collapsed across arousal level) and arousal dimensions (i.e., collapsed across valence level). This approach was adopted from Mickley Steinmetz and Kensinger (2009) as a way of examining the independent contributions of valence (negative versus positive) and arousal (high versus low).

A series of mixed factorial ANOVAs (Analysis of Variance) were conducted, with emotion as a within-subjects factor, defined as either valence (Negative, Positive, Neutral) or arousal (High Arousal, Low Arousal, Neutral), and group status (TEC, PTSD) as a between-subjects factor. These ANOVAs were used to examine: 1) *Subjective Ratings* of arousal and

valence (i.e., ratings provided by participants) and 2) *Memory Performance.* Memory performance was measured using the discrimination index (P_r) derived from the two-high threshold model of recognition memory (Snodgrass & Corwin, 1988), and by calculating the overall hit rate minus the false alarm rate. Hit rate was defined as the proportion of encoded items assigned an "old" response at recognition, whereas false alarm rate was defined as the proportion of new items assigned an "old" response.

Next, I conducted 3) *ROI analyses* of fMRI data using mixed factorial ANOVAs with subregion (BLA vs. CMA or SFA) included as an additional within-subjects factor[3]. For this set of analyses, in order to isolate activity related to successful emotional memory encoding, activity related to *neutral photos* was subtracted from emotional photos (i.e., "activation" associated with negative photos refers to the difference in activation between successfully recognized negative photos compared with the baseline comparison condition of successfully recognized neutral photos). To address the potential influence of comorbid depression on the fMRI-ROI data, I ran these analyses both without and with BDI-II scores as a covariate variable. Similarly, I conducted a set of 4) *Medication-Related Analyses,* where I added medication as an additional covariate to examine the potential role of medications on the fMRI-ROI data.

To further interrogate the nature of the significant fMRI-ROI findings, I ran a set of 5) *Regression Analyses* to determine whether subregional activation predicted PTSD symptom severity. In this set of analyses, the independent variables included BDI-II scores and activity within the BLA, CMA, and SFA, and the dependent variable was symptom severity, as indexed by total CAPS scores. Where indicated, effect sizes were interpreted using partial eta squared

[3] An omnibus ANOVA with all three subregions failed to reveal any interaction effects with Group. However, it is important to consider that these omnibus analyses may mask simple effects and interactions in the context of a priori hypotheses, which are better addressed using more targeted statistical analyses (Rosenow & Rosenthal, 1995, 1998)

(η_p^2), with a scale of .02, .13, and .26, reflecting small, medium, and large effect sizes, respectively. For follow-up testing, Hedge's *g* was used to correct for small sample size; effect sizes of .2, .5, and .8 reflected small, medium, and large effect sizes, respectively (Cohen, 1988). Results were interpreted both in terms of statistical significance (using a *p*-value of .05) and using effect sizes to assess the strength or magnitude of the results.

Chapter 5: Results

Subjective Ratings

In regards to the valence dimension, I submitted valence ratings collected from *participants* to a 2 (Group: PTSD, TEC) × 3 (Valence: Negative, Positive, Neutral) mixed-model ANOVA. The analysis yielded both a significant main effect of Valence, $F(2, 40) = 198.35$, $p < .001$, $\eta_p^2 = .91$; across both groups, negative photos ($M = 1.89$, $SD = .36$) were rated as more negative than neutral photos ($M = 2.94$, $SD = 0.36$) and positive photos were rated as more positive ($M = 3.63$, $SD = .37$) than neutral photos (all p's $< .001$). The analysis also revealed a significant Group × Valence interaction, $F(2, 40) = 3.32$, $p = .047$, $\eta_p^2 = .14$. A follow-up independent samples t-test revealed a marginally significant finding but with a large effect size, whereby the PTSD group tended to perceive the negative stimuli as more unpleasant than the TEC group, $t(20) = 1.94$, $p = .067$, $g = 0.79$ (see Figure 4)[4]. There were no group differences between the subjective valence ratings for the other two categories.

[4] A power analysis estimates 25 individuals per group would be required for this finding to reach significance with an alpha value of .05 and a desired power of .80.

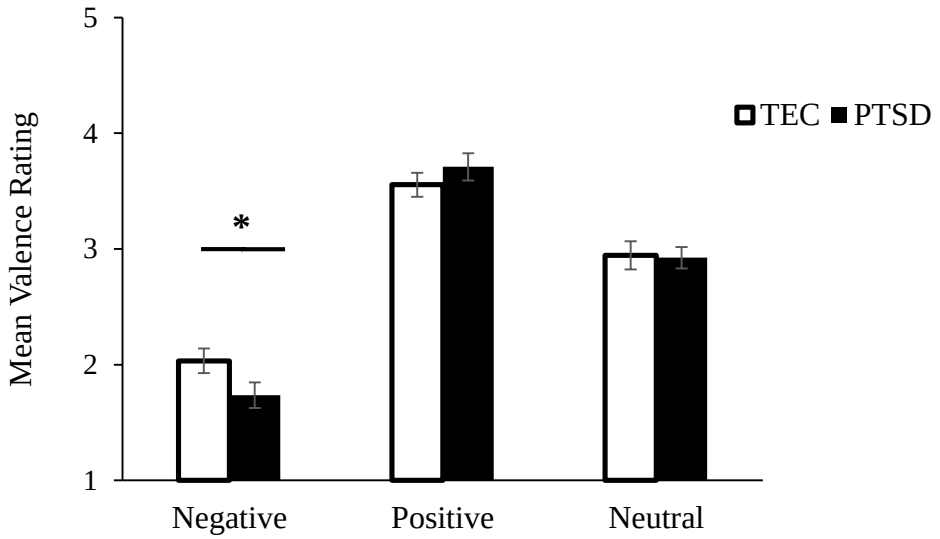

Figure 4. The PTSD group showed a marginally significant effect to perceive negatively valenced IAPS photos as more unpleasant than the TEC group (p = .067). Although the finding failed to reach significance, the magnitude of the effect was large *g = 0.79. Valence rating scale ranged from 1 (*very unpleasant)* to 5 (*very pleasant*). Error bars represent standard errors.

When I analyzed subjective valence ratings along the arousal dimension (Arousal: High Arousal, Low Arousal, and Neutral), there was a main effect of Arousal, $F(2, 40) = 18.06$, $p < .001$, $\eta_p^2 = .48$, but no Group × Arousal interaction, $F(2, 40) = 0.33$, $p = .718$, $\eta_p^2 = .02$. The main effect of Arousal revealed that all participants, irrespective of group, perceived the high arousing photos (M = 2.70, SD = 1.19) as more negative than either the low arousing (M = 2.82, SD = 1.14) or neutral photos (M = 2.94, SD = 1.70); and low arousing photos as more negative than the neutral photos (all p's < .01).

I then analyzed arousal ratings provided by *participants*. In regards to the valence dimension, the 2 (Group: PTSD, TEC) × 3 (Valence: Negative, Positive, Neutral) ANOVA revealed a main effect of Valence, $F(2, 40) = 49.46$, $p < .001$, $\eta_p^2 = .71$, and a marginally

significant Group × Valence interaction, $F(2, 40) = 2.85$, $p = .070$, $\eta_p^2 = .13$. However, post-hoc independent samples t-tests did not reveal any significant group differences in arousal ratings for any valence category (all p's > .10). When arousal ratings were analyzed according to the arousal dimension (Arousal: High Arousing, Low Arousing, Neutral), there was a main effect of Arousal, $F(2, 40) = 75.60$, $p < .001$, $\eta_p^2 = .79$, but no Group × Arousal interaction, $F(2, 40) = .70$, $p = .933$, $\eta_p^2 < .01$. All participants, irrespective of group, rated the high arousing items ($M = 2.89$, $SD = .83$) as more arousing than the low arousing ($M = 2.54$, $SD = .83$) and the neutral ($M = 1.83$, $SD = .82$) items, and low arousing items were rated as significantly more arousing than neutral items (all p's < .001).

Memory Performance

I submitted overall memory accuracy (P_r) scores to a 2 (Group: TEC, PTSD) × 3 (Valence: Negative, Positive, Neutral) ANOVA, which did not reveal any significant effects: There was no main effect of Group, $F(2, 20) = 2.02$, $p = .146$, $\eta_p^2 = .09$, and no Group × Valence interaction, $F(2, 40) = .07$, $p = .931$, $\eta_p^2 < .01$; see Figure 5. There were no significant effects when I analyzed memory accuracy according to the arousal dimension, including no main effect of Group, $F(2, 20) = .89$, $p = .423$, $\eta_p^2 = .04$, or Group × Arousal interaction, $F(2, 40) = .04$, $p = .965$, $\eta_p^2 < .01$.

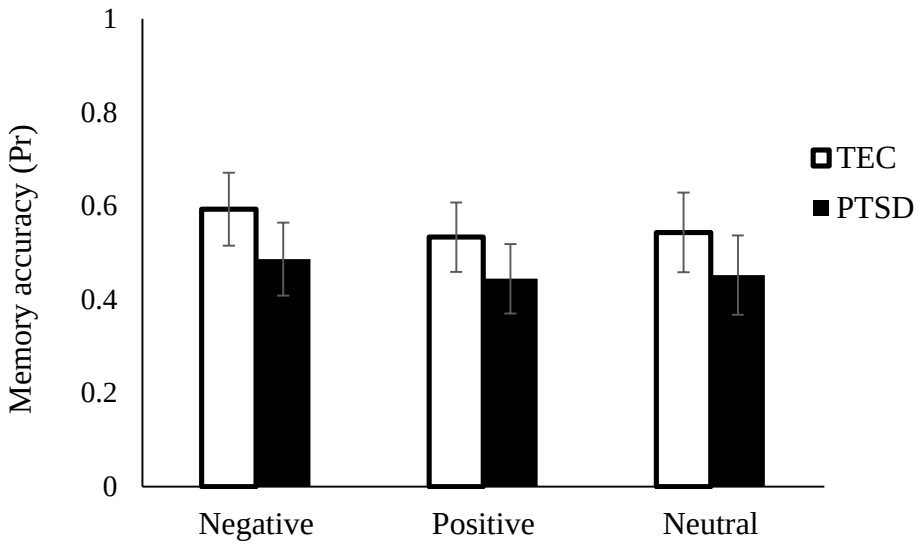

Figure 5. Analyses for overall memory accuracy failed to reveal any significant effects. Error bars represent standard errors.

ROI Analyses

With respect to valence, a 2 (Group: TEC, PTSD) × 2 (Valence: Negative, Positive) × 2 (Subregion: BLA, CMA) mixed-model ANOVA revealed a marginally significant main effect of Valence, $F(1, 20) = 3.45$, $p = .077$, $\eta_p^2 = .15$. The Group × Valence × Subregion interaction failed to meet conventional levels of significance testing, but this effect was small to medium, $F(1, 20) = 2.84$, $p = .108$, $\eta_p^2 = .12$. However, this 3-way interaction was significant when BDI-II scores were entered as a covariate, $F(1, 19) = 4.61$, $p = .045$, $\eta_p^2 = .20$. Follow-up pairwise contrasts using the depression-adjusted means revealed that the PTSD group showed significantly greater activation for successfully encoded negative relative to positive photos, and this effect was specific to the BLA and not the CMA region (see Figures 6 and 7).

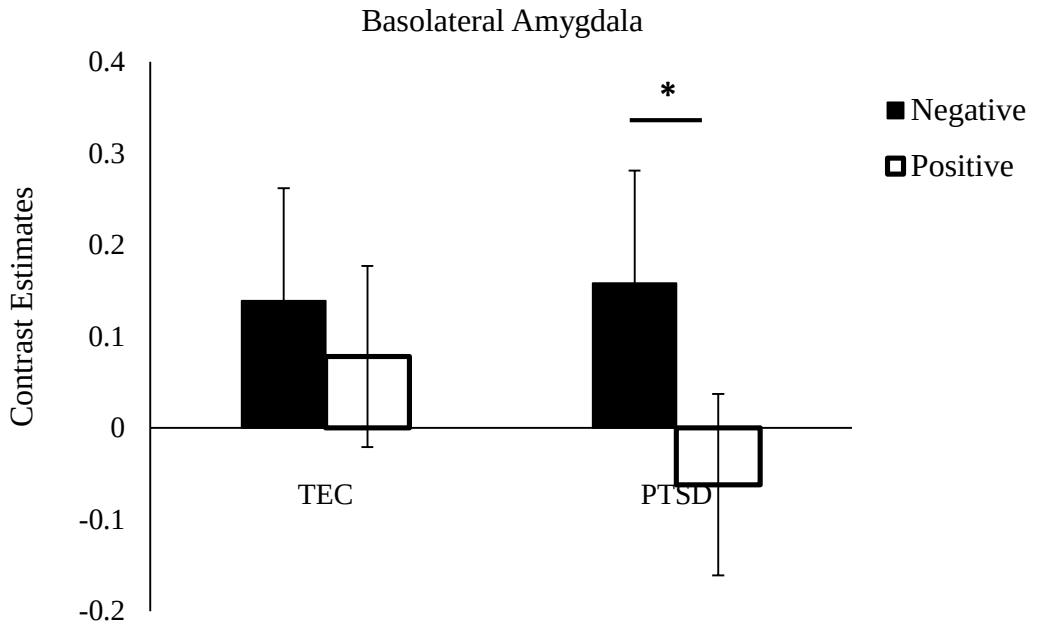

Figure 6. Mean activation in the BLA was greater for successfully encoded negative relative to positive photos (after subtracting activation for successfully encoded neutral photos from both valence categories) in the PTSD group but not in the TEC group.*p = .05. Error bars represent standard errors.

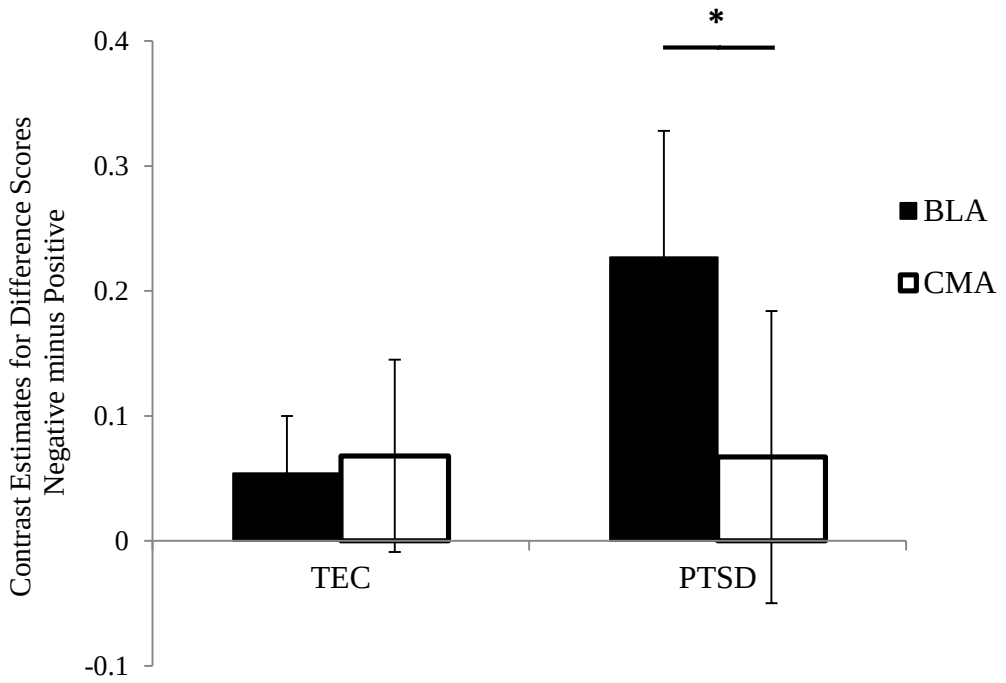

Figure 7. Difference scores whereby activity for successfully encoded positive photos was subtracted from activity related to successfully encoded negative photos. The PTSD group showed significantly greater activation for negative relative to positive photos in the BLA as compared to the CMA (*p = .034). No subregional difference was observed in the TEC group.

Next, I examined emotional-memory related activity between the BLA and SFA using a 2 (Group: TEC, PTSD) × 2 (Valence: Negative, Positive) × 2 (Subregion: BLA, SFA) mixed-model ANOVA. This analysis revealed a main effect of Valence, $F(1, 20) = 6.00$, $p = .024$, $\eta_p^2 = .23$, whereby activity was greater for negative items ($M = .23$, $SD = .04$) than positive items ($M = .18$, $SD = .03$). The analysis failed to reveal any other effects, including no main effect of Group,

$F(1, 20) = 27$, $p = .608$, $\eta_p^2 = .01$, and no Group × Valence × Subregion interaction, $F(1, 20) = .850$, $p = .367$, $\eta_p^2 = .04$. Similar results were obtained when BDI-II scores were included as a covariate in the analysis.

I then investigated group differences in subregional activation with respect to the arousal dimension: The 2 (Group: TEC, PTSD) × 2 (Arousal: High, Low) × 2 (Subregion: BLA, CMA) mixed-model ANOVA failed to reveal any significant effects, including no main effect of Arousal, $F(1, 20) = .03$ $p = .866$, $\eta_p^2 < .01$, or Group, $F(1, 20) = .13$, $p = .721$, $\eta_p^2 < .01$, and no Group × Arousal × Subregion interaction, $F(1, 20) = .003$, $p = .958$, $\eta_p^2 < .01$. Similarly, the mixed-model ANOVA comparing emotional memory-related activity in the BLA versus SFA also failed to reveal any significant effects: There was no main effect Arousal, $F(1, 20) = .03$, $p = .866$, $\eta_p^2 < .01$, no main effect of Group, $F(1, 20) = .27$, $p = .607$, $\eta_p^2 < .01$, and no Group × Arousal × Subregion interaction, $F(1, 20) = .37$, $p = .549$, $\eta_p^2 = .02$. Similar results were observed when BDI-II scores were included as a covariate.

Medication-Related Analyses

With the inclusion of medication use as an additional covariate, the 2 (Group: TEC, PTSD) × 2 (Valence: Negative, Positive) × 2 (Subregion: BLA, CMA) ANOVA revealed a marginally significant Subregion × Group interaction, $F(1, 18) = 3.89$, $p = .065$, $\eta_p^2 = .18$. Follow-up pairwise comparisons using the covariate-adjusted means revealed that only the PTSD group showed a significant difference between the BLA and CMA, $p = .038$, whereas no subregional difference was found in the TEC group, $p = .855$. Within the PTSD group, an independent samples t-test did not reveal any significant difference between those taking psychotropic medication ($M = .09$, $SD = .27$) and those not taking psychotropic medication ($M = .34$, $SD = .34$), $t(9) = 1.30$, $p = .225$, $g = .78$.

Regression Analyses

Given the significant findings regarding the valence dimension, a regression analysis was undertaken with BDI-II scores and subregional activation as predictors of PTSD symptom severity. With respect to activation for negative items, the overall regression model was significant, $R^2 = .54$, $p = .012$, with BDI-II scores significantly associated with PTSD symptom severity, $\beta = .669$, $t = 3.85$, $p = .001$. In addition, activity within the BLA just failed to meet conventional levels of statistical significance in predicting symptom severity, $\beta = .755$, $t = 1.99$, $p = .063$. In contrast, neither the CMA, $\beta = -.161$, $t = -0.46$, $p = .649$, nor the SFA, $\beta = -.618$, $t = -1.52$, $p = .146$, predicted PTSD symptom severity. Parallel analyses were undertaken for positiveitems. Similar to negative items, the overall regression model was significant, $R^2 = .32$, $p = .029$, and while BDI-II scores were significantly associated with symptom severity, $\beta = .715$, $t = 3.61$, $p = .002$, neither of the three subregions were significant predictors of PTSD symptom severity (all *p's* > .210).

Chapter 6: Discussion

6.1.0 Summary of Results

The aim of the current study was to use fMRI to assess whether PTSD, relative to TEC, was associated with greater BLA activity during encoding of emotional events. I hypothesized that PTSD would show greater amygdala activity during successful encoding of negative relative to positive events, and high arousing relative to low arousing events. I also hypothesized that this hyperactivity would be localized to the BLA as opposed to the other subregions. This hypothesis was based on the notion that PTSD symptoms are intimately tied to the learning and memory operations that are purported to be unique to the BLA.

The results of the current study revealed that, in contrast with the TEC group, PTSD was associated with significant greater BLA activity during successful encoding of negative relative to positive photos, therefore supporting one of my central hypotheses. As predicted, this effect was specific to the BLA, but only when compared with the CMA and not the SFA. Critically, this effect was statistically significant when depressive symptoms were controlled, suggesting that altered BLA activation supports a relatively specific association with PTSD symptoms. Corroborating this finding, only memory-related activity in the BLA showed a marginally significant effect toward independently predicting PTSD symptom severity. In contrast to the valence-related analyses, there were no subregional differences during successful encoding of high arousing versus low arousing photos for either group. These results suggest that the BLA may play a specialized role in the assessment of valence, with preferential processing for negative information in PTSD. In contrast, the degree of arousal appeared to be less of an influence on memory-related BLA function.

The behavioural results from this study provided converging support of the specificity of valence because the PTSD group exhibited a marginally significant, but large effect of perceiving negative photos as more unpleasant than the TEC group, and no group difference was observed when ratings were examined according to the arousal dimension. On the basis of the current findings, valence, rather than arousal, appears to be a more critical determinant of altered BLA activity during emotional memory encoding in PTSD.

6.2.0 Subregional Specificity of Amygdala Activation

To my knowledge, this is the first study to establish differences in task-related functional activation among amygdala subregions in PTSD. The current results support the proposition by Onur et al. (2009) that traumatic stress may selectively tune BLA neurons to respond to negative information, at the cost of neutral information. In the current study, only the PTSD group showed greater BLA activity during memory encoding of negative relative to positive events. Further, subregional specificity reliably emerged when the BLA was directly compared to the CMA. Functional differences between these two subregions converge with emerging findings from resting-state studies. Comparing a group of military veterans with PTSD to a TEC group, a recent study by Brown et al. (2014) used resting-state fMRI to assess group differences in BOLD activity at rest (i.e., when participants were not actively engaged in a task). Results indicated that the PTSD group had greater connectivity between the BLA and medial prefrontal regions while the TEC group had significantly greater connectivity between the BLA and inferior frontal gyrus. Critically, there were no group differences in functional connectivity stemming from the CMA. These resting-state findings suggest that altered functioning of the BLA, as observed in the current study, is likely supported by underlying changes in BLA connectivity that are unique to PTSD. The current study further demonstrated that, in contrast to the other two subregions,

memory-related activity in the BLA showed a marginally significant effect of independently predicting symptom severity in PTSD, as indexed by the CAPS. Although further replication is needed, the present findings suggest that altered BLA memory-related activity for negative information, may represent a unique biomarker of PTSD.

This separation of BLA versus CMA function is also consistent with the body of animal studies that have found functional dissociations between these two subregions, with fear learning and memory-based operations uniquely ascribed to the BLA (Da Cunha, Roozendaal, Vazdarjanova, & McGaugh, 1999; McGaugh 2000, 2004; Roozendaal & McGaugh, 1997; Tomaz, Dickinson-Anson, & McGaugh, 1992). In their assessment of functional subregional specificity in humans, some recent fMRI studies have compared the BLA to a corticomedial (CM) subdivision, which is approximated by averaging activity across the CMA and SFA subdivisions (Boll et al., 2013; Gamer, Zurowski,& Buchel 2010). This delineation is keeping with a deep (BLA) versus superficial (CM) nuclei classification of the amygdala complex (Bach, Weiskopf, & Dolan, 2011). Nonetheless, these studies, which have been conducted in healthy individuals, have demonstrated that whether in contrast to the pooled CM or separately defined CMA and SFA, the BLA mediates distinct functions including stimulus prediction (Boll et al., 2013) and responsiveness to pleasant and unpleasant auditory tones (Ball et al., 2007). The current study is the first to extend these functional dissociations to emotional memory in a clinical sample.

Important to note in my study is that the current finding of greater BLA activity during encoding of negative relative to positive items was only observed when comparing the CMA and not the SFA. Consistent with my propositions, delineating three separate subregions was important in the current study. Pooling across the CMA and SFA may have hindered the ability

to detect the observed differences between the BLA and CMA. Findings reported by Goossens et al. (2009) indicate that the SFA is selectively involved in processing social signals such as facial expressions of emotion. Congruent with this notion, many of the IAPS photos used in the current study were scenes containing interpersonal or social cues. As both negative and positive photos were equated for the number of photos containing people, it may be the case that both the BLA and SFA were equally recruited during memory encoding, but processing different types of information. The current results warrant further investigation of the unique roles of the BLA versus SFA as they pertain to memory encoding for emotional information.

6.2.1 The Influence of Comorbid Depression

The main finding of greater BLA activity in the PTSD group was more reliable when the variance related to depressive symptoms, as measured by the BDI-II, was taken into account. These findings indicate that the observed BLA effect in the PTSD group was not accounted for by comorbid depression. This finding supports the specific proposal that trauma-induced stress may convert a certain subset of neurons in the BLA to become hyper-responsive toward negative stimuli (Onur et al., 2009). Moreover, the current finding is consistent with the notion that threat-specific stress, as opposed to depression-related stress, may induce unique cellular and molecular changes in the BLA. Meta-analytic findings have shown that the hippocampus is reliably associated with decreased volume in depressed patients (McKinnon, Yucel, Nazarov, & MacQueen, 2009), whereas depression-related changes in amygdala volume have been more inconsistent (Hamilton, Siemer, & Gotlib, 2008). Animal studies also corroborate this notion; rodents exposed to chronic versus acute forms of stress show greater spine density across primary and secondary branches of BLA spiny neurons (Mitra, Jadha, McEwen, Vyas, & Chattarji, 2005). These stress-induced increases in dendritic growth in the BLA are distinct from

the dendritic aborizations that are observed in the CA3 subfield of the hippocampus (Vyas, Pillai, & Chattarji, 2004).

Important to note is that similar functional neuroimaging studies in PTSD have found exaggerated amygdala activity, even after controlling for depressive symptoms (e.g., Shin et al., 2005). In a study that directly compared a PTSD only group with a comorbid PTSD and major depression group, Lanius et al. (2007) used fMRI to examine neural activity during a script-driven symptom provocation task. The script involved remembering various sensations (olfactory, auditory, somatosensory, and visual) associated with the traumatic event. Whereas certain regions were more active in one group relative to the other (e.g., greater activation of the anterior cingulate in the comorbid group), no group differences were found in the amygdala. These findings further support the notion that the current BLA finding in the PTSD group is likely not attributed to depression-related stress.

In line with a proposal put forth by Lucassen and colleagues (2014), there appears to be increasing evidence that encoding of aversive experiences (e.g., being exposed to a traumatic event), is uniquely associated with both functional changes (i.e., greater activity during memory encoding of negative events), as shown in the current study, along with corresponding structural changes (i.e., increased dendritic growth; Mitra et al., 2005) in the BLA, and that these neural disturbances may facilitate the persistence of chronic symptoms observed in PTSD.

6.3.0 Independent Contributions of Valence and Arousal

In contrast to my hypotheses concerning valence, my predictions concerning arousal were not supported, because the PTSD group did not show greater BLA activity during successful encoding of high versus low arousing events. These results are considered surprising, given the robust influence arousal has on memory (Kensinger, 2004), and in the context of arousal-related

PTSD symptoms such as re-experiencing and hypervigilance (Boden et al., 2013). In contrast to arousal, valence appears to be a more critical determinant of BLA activity in PTSD during encoding of emotional events in this study, and this conclusion is supported by the behavioural results, which revealed a greater tendency for the PTSD group to rate negative photos as more negative as compared with the TEC group. Although this finding failed to reach significance, it was associated with a large effect size.

Other studies employing subjective ratings have found similar patterns with valence ratings. For instance, Hayes et al. (2011) found that combat veterans with PTSD showed a greater tendency to perceive negative photos as more negative than their TEC group. In another study, individuals with higher CAPS scores were more likely to rate face stimuli as more negative (Dickie et al., 2008). In a more recent study that directly compared arousal versus valence ratings, the authors similarly found that, although the PTSD group showed a tendency to rate scenes of daily events as more negative than the control group, there were no differences in arousal ratings (Baumann et al., 2013). Studies using IAPS photos have similarly failed to find any group differences in subjective arousal ratings (e.g., Brohawn et al, 2010). There is at least one study that has found higher arousal ratings in PTSD, albeit for a set of neutral photos (Zwissler et al., 2012). The overall pattern across these studies suggests that an altered subjective experience of valence, particularly for negative information, may be a more prominent behavioural feature of PTSD.

In addition to potential functional differences, it is also possible that structural abnormalities may be contributing to the lack of arousal-based findings. Shucard and colleagues (2012) observed that trauma re-experiencing scores were negatively correlated with brain volume for structures associated with autonomic arousal, including the amygdala. The lack of an

arousal effect may therefore relate to these types of structural abnormalities. Although many studies in PTSD have not found structural-related changes in the amygdala (see meta-analytic review by Woon & Hedges, 2009), some studies have found volumetric reductions (Karl et al., 2006; Morey et al., 2012; Pavlisa, Papa, Pavić, & Pavlisa, 2006; Rogers et al., 2009), and one recent study has even found increases in amygdala volume (Kuo, Kaloupek, & Woodward, 2012). Using hierarchical linear regression modelling, Kuo and colleagues (2012) found that different factors, including presence of early life trauma and severity of current trauma, influenced volumetric findings independent of PTSD diagnosis. Such factors could be contributing to the inconsistent findings across studies. The mitigating influence of these factors on amygdala structure and function, and their possible link to altered arousal responding in PTSD, warrant future investigation.

6.4.0 Relevance to Pathophysiological and Large-Scale Network Models of PTSD

A number of pathophysiological models of PTSD have been proposed over the years (Garfkinkel & Liberzon, 2009; Lanius et al., 2011; Paulus and Stein, 2006; Rauch et al., 1998). All these models implicate altered functioning of the amygdala and amygdala-related pathways in the pathogenesis of disorder. One such pathway involves the amygdala's bidirectional connections to areas of the medial prefrontal cortex (Ghashghaei & Barbas, 2002). The current study suggests that prefrontal signalling may specifically interact with the BLA during encoding of negative events, whereas the CMA may be less involved. Although speculative, this idea is supported by Brown et al. (2014) who recently found that as compared with TEC, PTSD was associated with greater connectivity between the BLA and medial prefrontal cortex.

Further assessment of these neural pathways can also be understood in the context of large-scale, neurocognitive networks, and studies using functional connectivity analyses (i.e.,

correlated activity among a group of brain regions). For instance, in a non-clinical sample, Roy et al. (2009) found that spontaneous activity in the BLA predicted bilateral activation in regions of the temporal lobe including the hippocampus, parahippocampus, and superior temporal gyrus. These regions of the temporal lobe reflect a critical hub in the default mode network, a large-scale brain network implicated in autobiographical recall and other self-referential processing (Andrews-Hanna, 2012; Spreng, Mar, & Kim, 2009). Bluhm et al. (2009) found that PTSD was associated with decreased connectivity between their selected default mode seed region (i.e., posterior cingulate cortex/precuneus) and the hippocampus/parahippocampal gyrus and the right amygdala. Given that the BLA, as opposed to other amygdala subregions, is functionally connected to default mode network areas such as the hippocampus and parahippocampus in healthy, non-clinical samples (Roy et al., 2010), the findings of the current study suggest that a specific pathway between the BLA and its hippocampal targets is also likely affected in PTSD. Dysfunction in this specific pathway may underlie a number of clinical features, including negative self-referential processing (Lanius et al., 2011), deficits in higher order cognition such as working memory (Daniels et al., 2010; Morgan, Terburg, Thornton, Stein, & van Honk, 2012), and impaired autobiographical recall (St. Jacques, Kragel, & Rubin, 2013), although this requires further investigation. The current findings further suggest that critical hubs of dysfunction, in the context of co-activation of networks or network switching (Sripada et al., 2012), may be localized to specific subregions such as the BLA. Based on the current and prior study findings, it seems that extant pathophysiological models of PTSD should be updated to include more thorough and comprehensive discussion of the BLA and its relation to PTSD symptoms.

6.5.0 Limitations and Future Directions

Although this is the first known study to provide evidence of altered BLA activity during emotional memory encoding in PTSD, interpretation of the findings should be considered in the context of the study's limitations. For instance, the nature of traumatic events across both groups varied, with a higher number of sexual assaults in the PTSD group. However, within the PTSD group, there was no significant difference in BLA activity when individuals associated with sexual trauma were directly compared with those without sexual trauma.[5] In contrast with the PTSD group, the TEC group had a greater number of vehicle accident-related traumas. It is not yet clear how amygdala function may be affected based on different trauma etiologies. It may be the case that physiological indices of trauma severity (e.g., the extent of molecular and cellular changes that are triggered following the initial trauma exposure), are more strongly connected to changes in the BLA, as opposed to the type of trauma per se, but further work is required to address these possibilities.

Epidemiological studies have shown that females exhibit almost a two-fold higher prevalence rate of PTSD than males (e.g., Tolin & Foa, 2006). Indeed, the majority of participants across both TEC and PTSD groups in the present study were females. However, within the PTSD group there was no significant difference between females and males with respect to the main BLA finding.[6] Thus, sex differences are unlikely to account for the observed increase in BLA responsivity during memory encoding of negative events. Nonetheless, functional neuroimaging studies in healthy adults have revealed differential involvement of the

[5]An independent samples t-test confirmed that PTSD participants with a history of sexual trauma (M =.12, SD = .35) did not differ from those without a sexual trauma (M = .32, SD = .35) in terms of the main BLA effect of greater activity to negative versus positive items, $t(9) = 1.03$, $p = .331$, $g = .52$.

[6]An independent samples t-test confirmed that female PTSD participants (M =.21, SD = .40) did not significantly differ from male PTSD participants (M = .24, SD = .24) with respect to the main BLA effect of greater activity to negative versus positive items $t(9) = .15$, $p = .884$, $g = .08$.

right (male) versus left (female) amygdala during successful encoding of emotionally stimuli (Cahill, Uncapher, Kilpatrick, Alkire, & Turner, 2006). On the basis of these sex-related lateralization findings, future work should aim to address whether recruitment of the BLA is differentially recruited by females and males affected by PTSD.

The current study failed to find any behavioural differences in memory between emotional items and neutral items. Whereas previous studies in non-clinical samples have found greater recognition accuracy for negative stimuli relative to neutral stimuli (e.g., Dolcos et al., 2004; Johansson, Mecklinger, and Treese, 2004; Mickley & Kensinger, 2008; Mickley Steinmetz & Kensinger, 2009), studies in PTSD have failed to reliably establish an emotional memory advantage that is distinct from controls, despite reporting different underlying neural correlates (Brohawn et al. 2010; Dickie et al., 2008; Hayes et al., 2011). It may be the case that the old/new paradigm commonly used in these studies does not target the appropriate memory processes. Emotion has been shown to specifically enhance recollective, rather than familiarity-based, processes at retrieval (Anderson, Yamaguchi, Grabski, & Lacka, 2006; Kensinger & Corkin, 2003; Patel, Girard, & Green, 2012; Sharot, Delgado, & Phelps, 2004; Sharot, Verfaellie, & Yonelinas 2007). That is, emotion enhances the feeling of reliving an event where associated contextual details are vividly recalled. Familiarity, rather, describes memory for an event, but without retrieval of supporting contextual details. Emotion-enhanced recollection has been associated with amygdala activation at both encoding and retrieval (Dolcos et al., 2005; Sharot et al., 2004; Phelps & Sharot, 2008). Future work should examine PTSD-related changes in recollection and familiarity and their relation to subregional amygdala function.

Another possible reason for the lack of an emotional memory effect may be related to the type of stimuli used. The photos used in the current study encompass a number of event types

(e.g., mutilated bodies, war-combat scenes, scenic views, partially nude individuals, inanimate objects) and were not necessarily specific to the trauma experienced by participants. Thus, it may be that non-trauma specific stimuli are not as sensitive to alterations in memory as compared with trauma-specific stimuli. However, this possibility also seems unlikely, because recent studies examining memory accuracy for trauma-related stimuli have failed to find robust group differences (Hayes et al., 2011; Whalley et al., 2013).

Another consideration of the current study was its inclusion of individuals taking medication. When medication use was included as an additional covariate in the analyses of interest, the main BLA effect in the PTSD group remained. There is building evidence that psychotropic medication can influence task-dependent changes in the BOLD signal, and this can be particularly challenging because clinical samples are often taking prescribed medication (Brown & Eyler, 2006). However, a qualitative review found that the vast majority of PTSD neuroimaging studies that have included medication-related analyses report no difference in functional brain changes when medication is statistically controlled or when compared to a no-medication group (Lanius et al., 2010a). The latter review additionally highlights findings from healthy controls that are particularly pertinent to the current study. For instance, Murphy, Norbury, O'Sullivan, Cowen, and Harmer (2009) demonstrated that a single oral dose of citalopram, as compared with placebo, reduced amygdala activity in response to viewing fearful faces in a group of healthy individuals. Moreover, this effect was specific to fearful faces and not observed in response to happy or neutral faces. Additional studies have also shown that administration of selective serotonin reuptuake inhibitors (SSRI) leads to a reduction in amygdala activity during emotional processing tasks under both explicit and implicit viewing conditions (Arce, Simmons, Lovero, Stein, & Paulus, 2008; Harmer, Mackay, Reid, Cowen, &

Goodwin, 2006). Because exaggerated amygdala activity is often cited as a unique biomarker of PTSD, it has been suggested that SSRI medications may exert their therapeutic effects by reducing this hyperactivity (Lanius et al., 2009). Of the 5 individuals in the PTSD group taking psychotropic medication, the majority (n = 4) were taking an SSRI. Within the PTSD group, there was no significant difference in BLA negative-related activation between those taking medication versus those not on medication. This suggests that the BLA effect in the PTSD group is likely not attributable to the higher proportion of psychotropic medication in this group.

Given the current findings, another possibility is that those taking SSRIs had lower depressive symptoms, and that when controlling for BDI-II scores, this enhanced the relations between PTSD symptom severity and the BLA. However, no correlation was observed between SSRI use and BDI symptom severity, thus also making this scenario unlikely. Nevertheless, future neuroimaging studies in PTSD, using larger sample sizes, should further interrogate the complex interplay between comorbid symptoms, SSRI use, and memory-related activity in the BLA.

6.6.1 Clinical Implications

There are several clinical implications to consider in light of the current findings. The regression analyses revealed that memory-related activity in the BLA, as opposed to the CMA or SFA, likely predicts PTSD symptom severity. Other studies examining the amygdala as a unitary structure have found that memory-related activity in the amygdala is positively correlated with current symptom severity, and not associated with decreased symptom severity across time (Dickie et al., 2011). Further, greater bilateral activation of the amygdala in response to masked fearful faces prior to cognitive-behavioural therapy has been associated with a poor response to treatment (Bryant et al., 2008). On the basis of the current findings, longitudinal studies should

be conducted in order to establish whether memory-related activity in the BLA predicts changes in symptom severity across time. Future studies are also needed to determine whether memory-related activity in the BLA could act as a key neural marker for identifying individuals that would be amenable or resistant to treatment.

Furthermore, it is interesting to consider that preferential recruitment of the BLA during encoding of negative photos may be related to negative self-referential processing that is often observed in PTSD. Prior studies have found that, relative to trauma-exposed controls, individuals with PTSD endorse a greater number of negative trait adjectives (e.g., abandoned, unlovable, despicable) and fewer positive trait adjectives as self-descriptive (Lanius et al., 2011). The relationship between the observed BLA effect and symptoms of negative self-referential processing should also be an area of future investigation.

Chapter 7: Concluding Remarks

The overall goal of this dissertation was to examine emotional memory-related activation across three discrete amygdala subregions in PTSD. The present findings extend prior work in this area, which has largely focused on examining the amygdala as a unitary structure and emotion as a singular, rather than a dimensional, construct. In this fMRI investigation, I demonstrated that, in contrast with the TEC group, the PTSD group exhibited greater BLA activity during encoding of successfully remembered negative relative to positive photos. This effect was specific to the BLA when compared with the CMA (but not the SFA) and was reliably observed after controlling for depressive symptoms. These findings suggest that activation of the BLA is strongly connected to memory encoding of negative-related experiences in PTSD. They also indicate that exaggerated amygdala activity, which is often cited as a critical neurobiological marker in PTSD, may be circumscribed to the BLA when learning and memory functions are

utilized. I further demonstrated that emotional memory-related activity in the BLA showed a marginally significant effect of independently predicting PTSD symptom severity. This finding was again, unique to the BLA, and not observed in the either the CMA or SFA.

Future neuroimaging work would benefit from further replication of these findings using larger sample sizes. Whether the present memory-based BLA finding is associated with changes in connectivity with other regions involved in emotional memory consolidation, also warrants further investigation. The present findings revealed that negative valence, as opposed with high arousal, was a critical determinant of the observed BLA effect. Future studies should aim to investigate whether this finding generalizes to other stimulus types beyond the IAPS photos. Moreover, the present findings call for further investigation of the relation between BLA function and encoding of negative experiences, to the expression of negative thoughts and emotions in PTSD.

Work from both animal and human studies have consistently shown that the amygdala plays a critical role in the consolidation of emotional memories. Changes in amygdala function are often implicated in PTSD as the underlying pathophysiology for a range of symptoms. To my knowledge, this is the first study to provide preliminary evidence that memory encoding of negative events in PTSD may be a unique function of the BLA, as opposed to the entire amygdala as a whole.

Appendix I: List of Abbreviations

ANOVA = Analysis of variance

BDI-II = Beck Depression Inventory-II

BLA = Basolateral amygdala

BOLD = Blood-oxygen-level dependent

CAPS = Clinician-Administered PTSD Scale

CMA = Centromedial amygdala

CM = Corticomedial amygdala

fMRI = Functional magnetic resonance imaging

IAPS = International affective picture system

Pr = Memory accuracy

PTSD = Posttraumatic stress disorder

ROI = Region of Interest

SFA= Superficial amygdala

SPM8 = Statistical Parametric Mapping, version 8

SSRIs = Selective serotonin reuptuake inhibitors

TEC= trauma-exposed controls

Appendix II: Voxelwise Whole Brain Analyses

As a secondary endeavour, I undertook a whole-brain analysis to examine those regions beyond the amygdala that were associated with successful encoding of photos. For these analyses, a Group × Valence interaction revealed clusters of activation in the frontal lobe, including the left anterior cingulate and right inferior frontal gyrus. Clusters of activation in the temporal lobe included the bilateral temporal pole, right amygdala, and right insula (see Table A and Figure A)[7]. A Group × Arousal interaction revealed clusters of activation in the frontal lobe, including the right postcentral gyrus and right inferior frontal gyrus. In the temporal lobe, there were clusters of activation in the left inferior temporal gyrus and right temporal pole. There was also a cluster of activation found in the parietal lobe, specifically within the left precuneus (see Table B).

Interestingly, amygdala activity was only associated with the Group × Valence analysis and not with the Group × Arousal analysis, which complements the valence-driven effects observed with the ROI analyses. Further investigation of the amygdala peak coordinate (24, 4, -20) across all four conditions reveals a similar pattern of greater activation for negative relative to positive photos for the PTSD group (see Figure B).

[7] Whole-brain results are presented for regions that survived a threshold of p = .05 (uncorrected) with a voxel extent of five contiguous voxels. Initial analyses with more stringent thresholds (i.e., with FDR $p < .05$) failed to yield significant clusters of activation. Thus, appropriate caution should be exercised when interpreting these results.

Table A

Whole-brain analysis for successfully encoded images related to the valence dimension

Brain Region	MNI coordinates (x,y,z)	Cluster size	p-Value* (uncorrected)	Z-value
Group X Valence interaction				
Frontal lobe				
Left precentral gyrus	-40, -20, 58	106	0.020	2.06
	-40, 30,58		0.024	1.98
	-38,-10,64	24	0.012	2.27
	-44,-8,60			
Left anteiror cingulate cortex	0,26,-6	17	0.017	2.12
Right SMA	4,-12,64	9	0.025	1.95
	8,20,62	9	0.031	1.87
Right inferior frontal gyrus	48,24,-12	5	0.043	1.71
Temporal lobe				
Right temporal pole	30,6,-20	40	0.018	2.11
Right amygdala	24, 4,-20		0.019	2.08
Left temporal pole	-20,6,-20	8	0.025	1.95
	-30,6,-24	6	0.027	1.93
	-34, 16,-28	5	0.026	1.94
Right Insula	40,-22,-2	8	0.027	1.93
Occipital lobe				
Right lingual gyrus	8,-36, -2	81	0.004	2.66
Right cerebellum	2,-44,-16		0.027	1.93
Cerebellum				
Right cerebellum	24,-36,-22	36	0.009	2.39
	18,-38,-16			2.24

*All effects were significant at p = .05(uncorrected), and five-voxel extent cluster size

Table B

Whole-brain analysis for successfully encoded images related to the arousal dimension

Brain Region	MNI coordinates (x,y,z)	Cluster size	p-Value* (uncorrected)	Z-value
Group X Arousal interaction				
Frontal lobe				
Right inferior frontal gyrus	60,22,16	12	0.034	1.82
Right superior frontal gyrus	18,26,60	6	0.028	1.91
Temporal lobe				
Left inferior temporal gyrus	-42,-12,-34	69	0.001	3.29
	-60,-4,30	16	0.017	2.12
	-62,-4,-28			
Right temporal pole	46,26,-28	9	0.016	2.20
Parietal lobe				
Right postcentral gyrus	16,-42,74	74	0.002	2.9
Left precuneus	-10,-56,38	30	0.015	2.18
Cerebellum				
Left cerebellum	-6,-38,-16	35	0.006	2.4
Right cerebellum	14,-34,-12	10	0.030	1.89

*All effects were significant at p = .05(uncorrected), and five-voxel extent cluster size

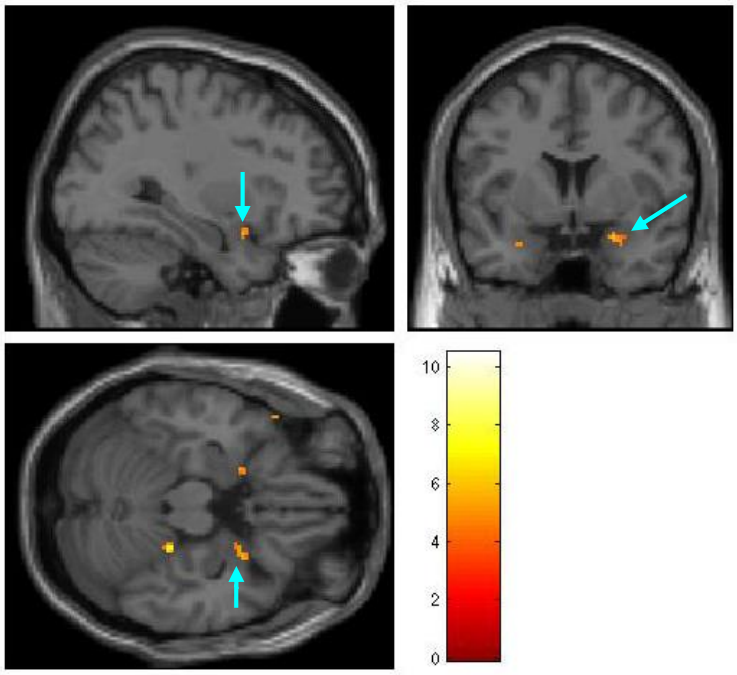

Figure A. Clusters of activity associated with the Group ×Valence interaction, including a cluster in the right amygdala (24, 4-20; denoted by turquoise arrows in all planes).

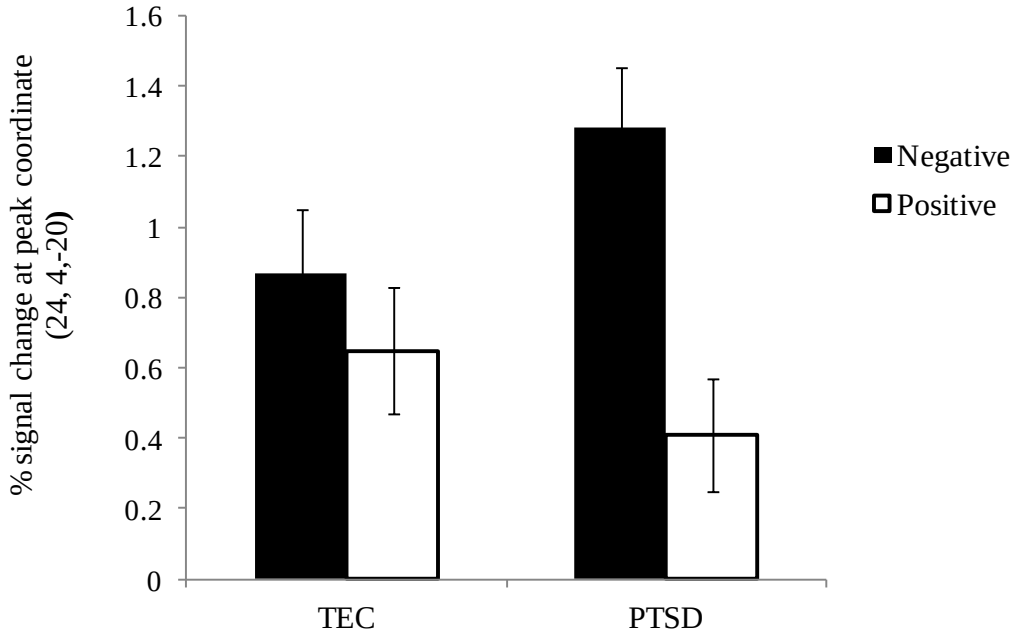

Figure B. Amygdala peak activation (24, 4,-20) extracted from whole brain Group × Valence interaction analysis. The pattern of activation converges with the ROI-specific finding of greater amygdala-related activity toward negative relative to positive photos in the PTSD, but not the TEC group. Error bars represent 95% confidence interval.

Appendix III: Checklist Form for IMPACT Lab Assessors

Recruitment for brain imaging study

***Instructions for assessors in IMPACT lab**: After you have completed your assessment, please go through the following check list. While you are not expected to ask your clients about items marked with an asterix (*), please indicate if you became aware of any of these conditions during the assessment. Once the form is completed, please relay all info to Nicole-Pukay Martin. (Alternatively, pass on to Marta, who will scan and send to NPM).*

Participant Study ID#: _____ **Date of Interview:** _____

Check List:	**Yes**	**No**
1. Experienced trauma that meets criterion A on CAPS	☐	☐
2. Has a CAPS score greater than 45?	☐	☐
a. If CAPS > 45, has 1-3-2 criteria been met?	☐	☐
3. Has a CAPS score less than 30?		
4. If your client's CAPS score falls between 30-45, please put actual score here: _____		
5. Meets criteria for current psychotic disorder?	☐	☐
6. Meets criteria for current substance abuse/dependence?	☐	☐

Did any of the following come up during your interview with the client?			**Don't Know**
7. *Does the client have a neurological disorder?	☐	☐	☐
8. *Does the client have a learning disorder?	☐	☐	☐
9. *Moderate to severe traumatic brain injury (LOC > 20 min)	☐	☐	☐

Check off which forms have been completed as part of your assessment:

☐ BDI (not administered in TRACE)

☐ PCL

☐ MINI

☐ SCID-IV

Appendix IV: Recruitment Notice to Eligible Participants

A Brain Imaging Study of Traumatic Experiences

Why?

The purpose of this study is to examine how the brain responds to viewing different types of emotional photos. The study is aimed at better understanding why some individuals with traumatic stress experience emotional and cognitive difficulties.

What?

Your participation would involve an interview, completing computerized and paper/pencil tasks, plus an MRI brain scan. You will be paid $40/h for your time and effort. The study will last 1-2 hours.

Who?

Participants who are currently enrolled in the TRACE (Tracking Reactions and Relationships After Critical Events) Study. Your decision to participate or not to participate in this brain imaging study will in no way affect your participation in the TRACE study. You must also:

- be 18-60 years of age
- not be pregnant, not have metal implants, and not be afraid of small spaces (due to MRI)

How?

Please reply to this e-mail as to whether or not you would like to be contacted for more information.

RYERSON UNIVERSITY

Appendix V: fMRI Telephone Screening Form

ID#: _____

	YES	NO
Have you ever experienced claustrophobia?	____	____
Have you ever had an epileptic seizure?	____	____
Have you ever had a head injury?	____	____
Have you had any visual disorders?	____	____
Can you see clearly at arms length without glasses (contacts are OK)?	____	____
Do you have a cardiac pacemaker or defibrillator?	____	____
Have you ever had surgery (if yes, describe below)?	____	____
Have you ever been injured by a metallic foreign body which was not removed?	____	____
Do you have cochlear (ear) implants?	____	____
Do you have dental work other than fillings (e.g., braces)?	____	____
Have you ever been a welder?	____	____
Have you ever been a soldier?	____	____
Are you taking any medications that could make you drowsy?	____	____

For women only:

	YES	NO
Do you have an IUD?	____	____
Are you pregnant or trying to conceive?	____	____
Are you breast-feeding?	____	____
Are you wearing an under-wire bra?	____	____

Additional comments:

_____

_____

Signature:_____Date: _____

fMRI Checklist

In addition to the above questions previously answered about metal in your body, it is also necessary that you do not enter the magnet with any metallic items. Before entering the magnet room, please:

	DONE
remove all jewellery	____
remove your wristwatch	____
remove *everything* from your pockets	____
keep your credit cards in the control room	____

Signature:_____Date: _____

Appendix VI: Brief Participant Interview

Participant ID#_____

Now I'd like to ask you some questions about you and your background. These questions will be stored securely and separately from your identifying information (consent form) and will only be linked through an arbitrary code #. I remind you that your participation is voluntary, so you have the right to answer as many or as few of these questions as you wish.

1. How old are you? _____ Date of Birth: _____
2. Height?_____ Weight? _____
3. Sex: F / M
4. Do you speak English fluently? _____
5. Do you have normal or corrected-to-normal vision? Y / N
6. Have you ever been diagnosed with a learning disability? Y / N
7. Have you ever lost consciousness (passed out or blacked out) for more than one hour? Y / N
   If yes: How long did it last? _____
8. Have you ever been diagnosed with a neurological condition (e.g., seizures, traumatic brain injury, dementia, etc.)? Y / N
9. Are you currently taking any medications to treat/help with mental health issues (e.g., antidepressants, anti-anxiety medications, etc.)? Y / N
10. Have you ever been diagnosed with a mental health disorder? Y / N

Appendix VII: Sample Consent Form

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Study: Brain Imaging Study
Investigators: Ronak Patel, MA, Psychology, Ryerson University
Todd Girard, PhD, Psychology, Ryerson University
Candice Monson, PhD, Psychology, Ryerson University
Study Location: Toronto Western Hospital (399 Bathurst St., Toronto, ON)

You would be one of approximately 60 people participating in this study. Before you give your consent to participate, it is important that you read the following information and ask as many questions as necessary to be sure you understand what you will be asked to do. This study will fulfil a graduate program requirement for Ryerson University's School of Graduate Studies.

Purpose: We are interested in how the brain responds when you are shown different types of photographs.

Procedure: By participating in this study, which will take approximately 1.5 to 2 hours, you will be asked to:

- Complete paper and pencil tests as well as computerized tests to assess cognitive skills (for example, problem-solving, memory, and attention)
- Complete paper-and-pencil surveys regarding your health and lifestyle
- Participate in a brain-scanning portion of the experiment for which you will be placed in a functional magnetic resonance imaging (fMRI) scanner. You will be presented with similar computerized tasks to those outside of the scanner requiring you to view a series of photographic stimuli that vary in emotional intensity. You will perform these tasks in two 15-minute sessions. You will be provided a short break in between these sessions; however, you will be required to remain in the scanner during this rest period. Prior to commencing the experiment, there will be an anatomical brain scan that also takes about ten minutes. After the scanning session, you will be asked to answer some questions about the tasks in the scanner.

Please note that you will be provided short breaks between test components as needed.

fMRI scan: The fMRI scan will be conducted at Toronto Western Hospital, where you will be accompanied by the experimenter. The fMRI technique involves lying in a large donut-shaped MRI machine that uses magnets and radiowaves to construct a picture of the brain on a computer. Before the scan begins, you will be asked to remove any magnetic metals that you are wearing, which may include items of clothing with metal parts. In this case, the MRI technician may ask that change into hospital gowns. For the procedure, you will be asked to lie on a padded bed that will be moved into a tunnel-like machine for the fMRI scan of your brain. During the

scan you will also be wearing display goggles for viewing the computer task. Thus, you will not be able to see the technician operating the machine or the investigators. However, there is an

intercom system that will allow you to talk with us at any time. Additionally, you will have a squeeze bulb with you in the scanner that you may press if you feel uncomfortable or if you want to discontinue the procedure at any time.

Setup and scanning can take up to one hour to complete. While you are in the scanner, you will be presented with the computerized tasks with photos of scenes and faces that vary in emotional intensity. You should try to remain as still as possible during the scans. Movements will not be dangerous to you in any way, but would blur the picture of your brain. You might hear moderately loud knocking or beeping during the scan when the MRI machine is in operation. Although you may find this to be unsettling, the machine cannot hurt you in any way. You will also be provided with ear plugs to minimize the noise.

Risks or Discomforts: You understand that the risks involved in participating in this study are small. At times during the study, you may become "mentally fatigued" or you feel frustrated or a little disappointed with your performance. However, whenever possible, you will be provided with rest breaks. It is also noted that the difficultly level on some tasks are designed to vary such that most people will make errors on the more difficult items. In addition, the personal nature of the questions during the interview or questionnaires may bring to mind unpleasant memories. You may also experience discomfort caused by viewing negative photographic stimuli. If you feel uncomfortable, you have the right to discontinue participation, either temporarily or permanently, at any time.

The fMRI scan is not associated with any known risks to your health and there is no evidence that there will be either short-term or long-term side effects. However, it is the policy of the hospital that you are not pregnant at the time of the fMRI scan. Prior to the fMRI you will be required to fill out a questionnaire to ensure that there should be no medical problems for you to participate in the study. There will be no needles, injections, drugs, or x-rays involved. However, because fMRI uses magnetism, you cannot have metal objects, metal fragments, or a pacemaker in your body or bring metal into the testing room. Some people feel uncomfortable or claustrophobic when inside the fMRI machine because it requires laying still for ~45 minutes in a small tunnel. That feeling passes quickly for most people, but you may ask us to stop testing at any time.

Because you will be in a tunnel-like machine that is equipped with a very strong magnet it is also the policy for fMRI scans that you:

1) do **NOT** have an implanted pacemaker
2) do **NOT** have any metal implants, pieces of shrapnel, aneurysm clips or wires in your head
3) do **NOT** have a history of anxiety problems related to closed spaces
4) do **NOT** have a history of heart problems

Benefits and Compensation: You understand that you will receive no direct benefit from participating in the study. However, the results of this study may benefit patients with post-

traumatic stress disorder in the future. In addition, you understand that you will receive $40.00 per hour for a total of $80 (2 hours in total), as compensation for your time and expenses.

Even though fMRI is a type of brain scan, it is not the kind of brain scan that a medical doctor would use to find out if there is a medical problem in your brain. If you are concerned that there might be a problem in your brain, you should make an appointment with your regular doctor immediately. Do not rely on this study to tell you about the medical status of your brain.

Confidentiality: Information learned about you in this study is confidential and will not be available to anyone except investigators. Note however, that the MR technicians at the Toronto Western Hospital require that they keep a secured copy of your fMRI screening form. Confidentiality will be protected to the extent permitted by law (i.e., you disclose that you are going to hurt yourself or someone else, are involved in any form of child abuse, or that you were sexually abused by a healthcare worker). If any unexpected medical findings arise from the results of the procedures involved in the project, we will recommend that you have a follow-up health assessment and we will provide all the relevant information to the healthcare provider that you specify. You will not be identified in any way in reports or presentations, which may arise from the study. You understand that data collected as part of your participation in the TRACE (Tracking Reactions and Relationships After Critical Events) study (REB 2011-067) may be shared with the current study. However, all data will be identified with ID codes only and stripped of any identifying information. If, for whatever reason, you do not fit the eligible profile we are seeking for this study, then all of your data will be destroyed. However, in order to track reasons for such exclusion, a coded list (with only ID codes and abstract codes representing reasons) will be kept securely and separately from any identifying information. Moreover, your information will not be disclosed. The study data will be stored in a locked cabinet and on a password protected computer in a research lab (105 Bond Street) with restricted access; only the primary investigators and research assistants supervised by the primary investigators will have access to the data. The data will be stored for at least 5 years, after which it will be confidentially shredded.

Withdrawal: Participation in this study is voluntary. At any particular point in the study, you may refuse to answer any particular question. You have the right to withdraw from the study at any time without explaining your reasons to do so without penalty or loss of benefits to which you are allowed. Your choice of whether or not to participate will in **no way** have any bearing on your participation in the TRACE (Tracking Reactions and Relationships After Critical Events) study (REB 2011-067). Your choice of whether or not to participate will also not affect your future relations with Ryerson University or Toronto Western Hospital.

Questions: You are encouraged to ask any question that you have about the study and all your questions will be answered. If you have any questions about the research now, please ask. If you have questions later about the research, you may contact the investigator and if you have questions regarding your rights as a human subject and participant in this study, you may contact the Ryerson University Research Ethics Board for information (contact information on next page).

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By signing this form you indicate that you have discussed the study with Ronak Patel and/or his research associate, who has explained the purpose, procedures, and risks of the study, and has answered your questions about it.

If you have any further questions about the study or about your rights as a participant, you may telephone Ronak Patel, Dr. Todd Girard (416-979-5000 x2192 (lab) or x2646 (office)), or Dr. Candice Monson ((416-979-5000 x6209). If you still have any questions about your rights as a participant, you may contact the Research Ethics Board, c/o Office of the Vice President, Research and Innovation, Ryerson University, 350 Victoria Street, Toronto, ON M5B 2K3, 416-979-5042.

You understand that you have the right to withdraw from the study at any time and that the information obtained about you is confidential. In any scientific report on the study the data will be presented without revealing participant identity. You have been told that by signing this consent agreement you are not giving up any of your legal rights.

You acknowledge that you have been given a copy of this consent form.

You agree to participate in this study.

Would you also like to be re-contacted for future studies in Psychology?: Yes / No

_____ _____

Participant's signature Date

_____

Participant's name (please print)

_____ _____

Witness Investigator Signature (required only if witness is not a primary investigator)

Appendix VIII: Sample IAPS Stimuli

Negative; High Arousal

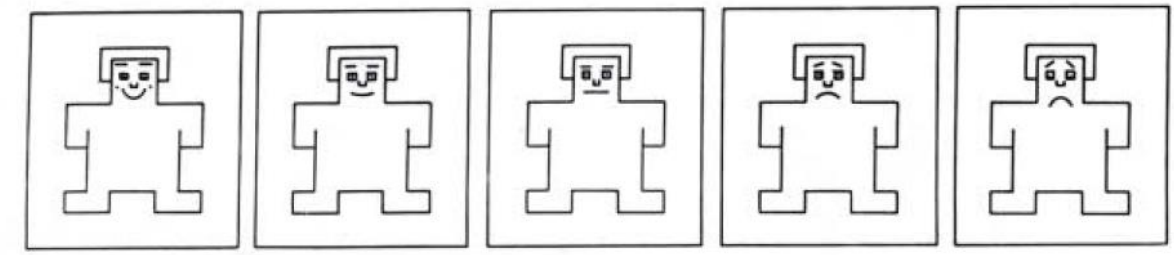
Negative; Low Arousal

Positive; High Arousal

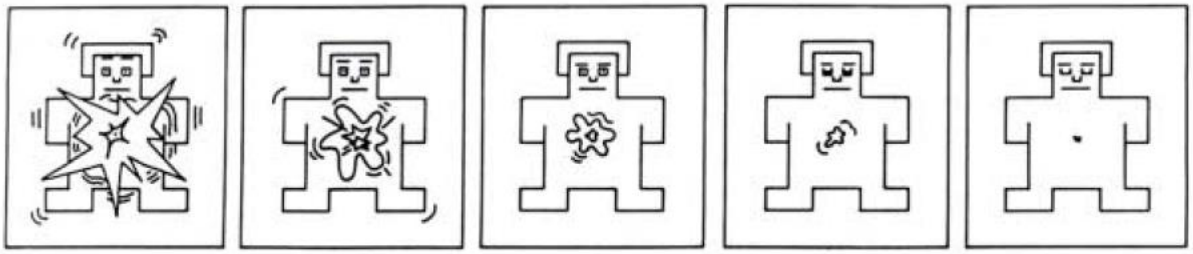
Positive; Low Arousal

Neutral

Appendix IX: Self-Assessment Manikin Scales: Subjective Ratings for Valence and Arousal



Valence



Arousal

Appendix X: Participant Debriefing Form

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You have participated in a research study conducted by Mr. Ronak Patel and Drs. Todd Girard and Candice Monson from the Department of Psychology at Ryerson University.

Traumatic Stress: A Brain Imaging Study

Background Information:

Individuals who are exposed to a traumatic event can often experience symptoms that significantly interfere with important activities such as going to work or spending time with family and friends. One widely-used option for treatment, cognitive-behavioural therapy (CBT), aims to reduce the level of anxiety connected to trauma-related thoughts, attitudes, and beliefs. Findings from brain imaging studies reveal significant alterations in brain structure and function in trauma-exposed individuals may be directly tied to advancing current treatment interventions such as CBT. More specifically, the amygdala, a region commonly referred to as the "emotional centre" of the brain, may play key role in the development and maintenance of trauma-related symptoms. Previous research suggests that specific parts of the amygdala play specialized roles in our memory for unpleasant events and may be directly linked to trauma-related symptoms.

Purpose of the Study: The current study provides a better understanding of the links between the amygdala, memory for emotional information, and traumatic stress. For this purpose, persons with and without traumatic stress are shown a series of photographic scenes and facial expressions varying in emotional intensity while in a brain scanner to measure brain activity particularly in amygdala subregions. Subsequently, memory for the scenes is tested to further characterize the biological basis underlying altered memory functioning intrauma-exposed individuals. We believe that this study will provide important information for further understanding the nature of symptoms linked to traumatic memories.

Design of the Study: You are one of 60 participants in this study. You were asked to view and make decisions about different photos of scenes and faces and later given a memory test for these photos. Some of the photos were presented at a very rapid rate and you may not have actually noticed them being presented. This type of presentation was undertaken as it has been shown to maximize our ability to measure amygdala activity in trauma-exposed individuals. You were also not explicitly told that you were later going to receive a memory test on task pictures because we did not want individuals to use special strategies that could potentially affect memory performance. Different strategies are known have to different effects on memory performance, thus, we wanted to minimize the possibility that such strategies would be used.

Expected Results: We expect that persons with trauma-exposure will show heightened activity in a particular part of the amygdala known as the BLA as compared to other amygdala subregions. We further expect that BLA activity will predict whether emotionally arousing photos will later be remembered. Lastly, we

expect that a reduction trauma-related symptoms following CBT will be associated with a significant reduction in BLA activity.

Questions and Concerns: If your participation in this study raises psychological concerns and you are currently enrolled in the TRACE (Tracking Reactions and Relationships After Critical Events) Study at Ryerson University, please contact Dr. Candice Monson (416-979-5000 x6209; candice.monson@psych.ryerson.ca). If you are a Ryerson student and your participation in this study raises psychological concerns that you would like to discuss, please contact the Centre for Student Development and Counselling (CSDC) located in JOR-07C, 416-979-5195, csdc@ryerson.ca. Through the CSDC, professional counsellors are available to talk to full and part-time Ryerson students on a variety of personal, career or academic concerns free of cost. The CSDC can also suggest community resources and provide crisis support. These services are confidential. For more information, you can visit: http://www.ryerson.ca/counselling/index.html.

If you have questions about this study or would like to remove your data from the study, please contact one of the investigators listed below. You may also contact us after August 2013 if you would like to receive a copy of the results from this study.

Brain Imaging & Memory Lab	416-979-5000 x2192
Ronak Patel	ronak.patel@psych.ryerson.ca
Dr. Todd Girard	tgirard@psych.ryerson.ca
Dr. Candice Monson	candice.monson@psych.ryerson.ca

If you having any questions regarding your rights as a human subject and participant in this study, you may contact the Ryerson University Research Ethics Board for information: Ryerson Ethics Board, c/o Office of the Vice President, Research and Innovation, Ryerson University,350 Victoria Street, Toronto, ON M5B 2K3; 416-979-5042.

References for further reading:

Bryant et al. (2008). Amygdala and ventral anterior cingulate activation predicts treatment response to cognitive behavior therapy for post-traumatic stress disorder. *Psychological Medicine, 38*, 555-561.

Garfinkel, S. N., & Liberzon, I. (2009). Neurobiology of PTSD: A review of neuroimaging findings. *Psychiatric Annals, 39*, 370-381.

Onur et al. (2009). Noradrenergic enhancement of amygdala responses to fear. *Social Cognitive and Affective Neuroscience, 4*, 119-126.

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References

Adolphs, R., Cahill, L., Schul, R., & Babinsky, R. (1997). Impaired declarative memory for emotional material following bilateral amygdala damage in humans. *Learning & Memory, 4*, 291–300. doi: 10.1101/lm.4.3.291

Agren,T., Engman, J., Frick, A., Björkstrand, J., Larsson, Larsson, E-M., … Fredrikson, M. (2012). Disruption of reconsolidation erases a fear memory trace in the human amygdala. *Science, 337*, 1550 – 1552. doi: 10.1126/science.1223006

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Amunts, K., Kedo, O., Kindler, M., Pieperhoff, P., Mohlberg, H., Shah, N.J., … Zilles, K. (2005). Cytoarchitectonic mapping of the human amygdala, hippocampal region and entorhinal cortex: Intersubject variability and probability maps. *Anatomy and Embryology, 210*, 343–352. doi: 10.1007/s00429-005-0025-5

Anderson, A. K., Yamaguchi, Y., Grabski, W., & Lacka, D. (2006). Emotional memories are not all created equal: Evidence for selective memory enhancement. *Learning and Memory, 13*, 711-718. doi: 10.1101/lm.388906

Andrews-Hanna, J. R. (2012). The adaptive role of the default network in internal mentation. *The Neuroscientist, 18,* 251–270. doi: 10.1177/1073858411403316

Arce, E., Simmons, A. N., Lovero, K. L., Stein, M. B., & Paulus, M. P. (2008). Escitalopram effects on insula and amygdala BOLD activation during emotional processing. *Psychopharmacology, 196*, 661-672. doi: 10.1007/s00213-007-1004-

Armony, J. L., Corbo, V., Clement, M. H., & Brunet, A. (2005). Amygdala response in patients with acute PTSD to masked and unmasked emotional facial expressions. *American Journal of Psychiatry 162,* 1961–1963. doi:10.1176/appi.ajp.162.10.1961

Bach, D. R., Weiskopf, N. & Dolan, R. J. (2011). A stable sparse fear memory trace in human amygdala. *Journal of Neuroscience, 31,* 9383–9389. doi: 10.1523/JNEUROSCI.1524-11

Ball, T., Rahm, B., Eickhoff, S. B., Schulze-Bonhage, A., Speck, O., & Mutschler, I. (2007). Response properties of human amygdala subregions: Evidence based on functional MRI combined with probabilistic anatomical maps. *PLoS One,* 2, e307. doi: 10.1371/journal.pone.000030

Baumann, M., Zwissler, B., Schalinski, I., Ruf-Leuschner, M., Schauer, M., & Kissler, J. (2013). Directed forgetting in post-traumatic-stress-disorder: a study of refugee immigrants in Germany. *Frontiers in Behavioral Neuroscience, 7*: 94. doi: 10.3389/fnbeh.2013.00094

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry, 4,* 561–571. doi:10.1001/archpsyc.1961.01710120031004.

Blake, D. D., Weathers, F. W., Nagy, L. M., Kaloupek, D. G., Gusman, F. D., Charney, D. S., & Keane, T. M. (1995). The development of a clinician-administered PTSD scale. *Journal of Traumatic Stress, 8,* 75–90. doi: 10.1007/BF02105408

Bluhm, R. L., Williamson, P. C., Osuch, E. A., Frewen, P. A., Stevens, T. K., Boksman, K., … Lanius, R. A. (2009). Alterations in default network connectivity in posttraumatic stress disorder related to early-life trauma. *Journal of Psychiatry Neuroscience, 34,*187-194. Retrieved from:

http://ezproxy.lib.ryerson.ca/login?url=http://search.proquest.com.ezproxy.lib.ryerson.ca/docview/217293530?accountid=13631

Boden, M. T., Westermann, S., McRae, K., Kuo, J., Alvarez, J., Kulkarni, M. R., … Bonn-Miller, M. O. (2013). Emotion regulation and Posttraumatic Stress Disorder: A prospective investigation. *Journal of Social and Clinical Psychology, 32*, 296-314. doi: 101521jscp2013323296

Boll, S., Gamer, M., Gluth, S., Finsterbusch, J., & Büchel, C. (2013). Separate amygdala subregions signal surprise and predictiveness during associative fear learning in humans. *European Journal of Neuroscience, 37*, 758–767. doi: 10.1111/ejn.12094

Bremner, J. D., Narayan, M., Staib, L. H., Southwick, S. M., McGlashan, T., & Charney, D. S. (1999). Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. *American Journal of Psychiatry, 156*, 1787-1795. Retrieved from http://search.proquest.com/docview/220487035/6B1A8EF2927440CCPQ/1?accountid=13631

Brewin, C. R., Kleiner, J. S., Vasterling, J. J., & Field, A. P. (2007). Memory for emotionally neutral information in posttraumatic stress disorder: A meta-analytic investigation. *Journal of Abnormal Psychology,. 116*, 448-63. doi: 10.1037/0021-843X.116.3.4

Brohawn, K. H., Offringa, R., Pfaff, D. L., Hughes, K. C., & Shin, L. M. (2010). The neural correlates of emotional memory in posttraumatic stress disorder. *Biological Psychiatry, 68*, 1023-1030. doi: 10.1016/j.biopsych.2010.07.018

Brown, G. G., & Eyler, L. T. (2006). Methodological and conceptual issues in functional magnetic resonance imaging: applications to schizophrenia research. *Annual Review of Clinical Psychology, 2, 51-81*. doi: 10.1146/annurev.clinpsy.2.022305.095241

Brown, V. M., LaBar, K. S., Haswell, C. C., Gold, A. L., Mid-Atlantic MIRECC Workgroup, McCarthy, G., & Morey, R. A. (2014). Altered resting-state functional connectivity of basolateral and centromedial amygdala complexes in posttraumatic stress disorder. *Neuropsychopharmacology, 39*, 351-359. doi: 10.1038/npp.2013.197

Bryant, R. A., Felmingham, K., Kemp, A., Das, P., Hughes, G., Peduto, A., & Williams, L. (2008). Amygdala and ventral anterior cingulate activation predicts treatment response to cognitive behaviour therapy for post-traumatic stress disorder. *Psychological Medicine, 38*, 555-561. doi:10.1017/S0033291707002231

Cahill, L., Uncapher, M., Kilpatrick, L., Alkire, M. T., & Turner, J. (2004). Sex-related hemispheric lateralization of amygdala function in emotionally influenced memory: An FMRI investigation. *Learning & Memory, 11,* 261–266. doi: 10.1101/lm.70504

Cahill, L., Haier, R. J., Fallon, J., Alkire, M., Tang, C., Keator, D., … McGaugh, J. L. (1996). Amygdala activity at encoding correlated with long-term, free recall of emotional information. *Proceedings of the National Academy of Sciences of the United States of America,* 93, 8016–8021. doi: 10.1073/pnas.93.15.8016

Canli, T., Zhao, Z., Brewer, J., Gabrieli, J. D., & Cahill, L. (2000). Event-related activation in the human amygdala associates with later memory for individual emotional experience. *Journal of Neuroscience, 20,* RC99, 1–5. Retrieved from: http://ezproxy.lib.ryerson.ca/login?url=http://search.proquest.com.ezproxy.lib.ryerson.ca/docview/619679275?accountid=13631

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Mahwah, NJ: Lawrence Erlbaum.

Critchley, H., Daly, E., Phillips, M., Brammer, M., Bullmore, E., Williams, S.,…Murphy, D. (2000). Explicit and implicit neural mechanisms for processing of social information from facial expressions: A functional magnetic resonance imaging study. *Human Brain Mapping, 9,* 93–105. doi: 10.1002/(SICI)1097-0193(200002)9:2<93::AID HBM4>3.0.CO;2-Z

Cukor. J., Olden, M., Lee, F. S., & Difede, J. (2010). Evidence-based treatments for PTSD, new directions, and special challenges. *Annals of the NY Academy of Science, 1208,* 82-89. doi: 10.1111/j.1749-6632.2010.05793.x.

Da Cunha, C., Roozendaal, B., Vazdarjanova, A., & McGaugh, J. L. (1999). Microinfusions of flumazenil into the basolateral but not the central nucleus of the amygdala enhance memory consolidation in rats. *Neurobiology of Learning and Memory, 72,* 1–7. doi: 10.1006/nlme.1999.3912

Dale, A. (1999). Optimal experimental design for event-related fMRI. *Human Brain Mapping, 8,* 109–114. doi: 10.1002/(SICI)1097-0193(1999)8:2/3<109::AID-HBM7>3.0.CO;2-W

Daniels, J. K., McFarlane A. C., Bluhm, R. L., Moores, K. A., Clark, C. R., Shaw, M. E., … Lanius, R. A. (2010). Switching between executive and default mode networks in posttraumatic stress disorder: alterations in functional connectivity. *Journal of Psychiatry and Neuroscience, 35,* 258–266. doi: 10.1503/jpn.090175

Dębiec, J., Bush, D. E., & LeDoux, J. E. (2011). Noradrenergic enhancement of reconsolidation in the amygdala impairs extinction of conditioned fear in rats--a possible

mechanism for the persistence of traumatic memories in PTSD. *Depression & Anxiety, 28*, 186–193. doi: 10.1002/da.20803

Dickie, E., Brunet, A., Akerib, V., & Armony, J. (2008). An fMRI investigation of memory encoding in PTSD: influence of symptom severity. *Neuropsychologia, 46*, 1522– 1531. doi: 10.1016/j.neuropsychologia.2008.01.007

Dickie, E., Brunet, A., Akerib, V., & Armony, J. (2011). Neural correlates of recovery from post-traumatic stress disorder: A longitudinal fMRI investigation of memory encoding. *Neuropsychologia, 49*, 1771–1778. doi: 10.1016/j.neuropsychologia.2011.02.055

Dolcos, F., LaBar, K. S., & Cabeza, R. (2005). Remembering one year later: Role of the amygdala and the medial temporal lobe memory system in retrieving emotional memories. *Proceedings of the National Academy of Sciences of the United States of America, 102*, 2626–2631. doi: 10.1073/pnas.0409848102

Ehlers, A., & Clark, D. M., (2000). A cognitive model of posttraumatic stress disorder. *Behaviour Research and Therapy, 38*, 319–345. doi: 10.1016/S0005-7967(99)00123-0

Eickhoff, S.B., Stephan, K. E., Mohlberg, H., Grefkes, C., Fink, G. R, Amunts, K., & Zilles, K. (2005). A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *Neuroimage, 25*, 1325–1335. doi: 10.1016/j.neuroimage.2004.12.034

Etkin, A., Prater, K. E., Schatzberg, A. F., Menon, V., & Greicius, M. D. (2009). Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in generalized anxiety disorder. *Archives of General Psychiatry, 66*, 1361–1372. doi: 10.1001/archgenpsychiatry.2009.104

Falconer, E., Bryant, R., Felmingham, K. L., Kemp, A. H., Gordon, E., Peduto, A., … Williams, L. M. (2008). The neural networks of inhibitory control in posttraumatic stress disorder. *Journal of Psychiatry and Neuroscience, 33*, 413–422. Retrieved from: http://ezproxy.lib.ryerson.ca/login?url=http://search.proquest.com.ezproxy.lib.ryerson.ca/docview/217290609?accountid=13631

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (2002a). *Structured clinical interview for DSM-IV-TR axis I disorders, research version, patient edition with psychotic screen (SCID-I/P W/PSY SCREEN).* New York, NY: Biometrics Research.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (2002b). *Structured clinical interview for DSM-IV-TR axis I disorders, research version, non-patient edition (SCID-I/NP).* New York, NY: Biometrics Research.

Frank, J. E., & Tomaz, C. (2003). Lateralized impairment of the emotional enhancement of verbal memory in patients with amygdalahippocampal lesion. *Brain and Cognition,* 52, 223–230. doi: 10.1016/S0278-2626(03)00075-7

Fredrickson, B. L., & Branigan, C. (2005). Positive emotions broaden the scope of attention and thought action repertoires. *Cognition and Emotion, 19*, 313–332. doi: 10.1080/026999304410002

Gamer, M., Zurowski, B., & Buchel, C. (2010). Different amygdala subregions mediate valence-related and attentional effects of oxytocin in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *107,* 9400–9405. doi: 10.1073/pnas.1000985107

Garfinkel, S. N., & Liberzon, I. (2009). Neurobiology of PTSD: A review of neuroimaging findings. *Psychiatric Annals, 39*, 370–381. Retrieved from:

http://ezproxy.lib.ryerson.ca/login?url=http://search.proquest.com.ezproxy.lib.ryerson.ca/docview/217036472?accountid=13631

Ghashghaei, H. T., & Barbas, H. (2002). Pathways for emotion: interactions of prefrontal and anterior temporal pathways in the amygdala of the rhesus monkey. *Neuroscience*, 115, 1261-1279. doi: 10.1016/S0306-4522(02)00446-3

Glover, E. M., Phifer, J. E., Crain, D. F., Norrholm, S. D., Davis, M., Bradley, B., … Jovanovic, T. (2011). Tools for translational neuroscience: PTSD is associated with heightened fear responses using acoustic startle but not skin conductance measures. *Depression & Anxiety, 28*, 1058-1066. doi: 10.1002/da.20880

Goddard, G. V. (1964). Amygdaloid stimulation and learning in the rat. *Journal of Comparative and Physiological Psychology, 58*, 23–30. doi: http://dx.doi.org.ezproxy.lib.ryerson.ca/10.1037/h0049256

Gold, P. E., & McGaugh, J. L. (1975). A single-trace, two process view of memory storage processes. In: Deutsch, D., Deutsch, J.A. (Eds.), *Short-Term Memory*. Academic Press, New York, pp. 355–378.

Gold, P. E., & van Buskirk, R. B. (1978). Posttraining brain norepinephrine concentrations: Correlation with retention performance of avoidance training and with peripheral epinephrine modulation of memory processing. *Behavioral. Biology, 23,* 509–520. doi: 10.1016/S0091-6773(78)91614-0

Goossens, L., Kukolja, J., Onur, O. A., Fink, G. R., Maier, W., Griez, E., ... Hurlemann, R. (2009). Selective processing of social stimuli in the superficial amygdala. *Human Brain Mapping, 30,* 3332-3338. doi: 10.1002/hbm.20755

Hamann, S. B., Eli, T. D., Grafton, S. T., & Kilts, C. D. (1999). Amygdala activity related to enhanced memory for pleasant and aversive stimuli. *Nature Neuroscience, 2*, 289–303. doi: 10.1038/6404

Hamilton, J. P., Siemer, M., & Gotlib, I. H. (2008). Amygdala volume in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. *Molecular Psychiatry, 13*, 993-1000. doi: 10.1038/mp.2008.57

Hariri A. H., Bookheimer, S. Y., & Mazziotta, J. C. (2000). Modulating emotional responses: Effects of a neocortical network on the limbic system. *NeuroReport , 11*, 43–8. doi: 10.1097/00001756-200001170-00009

Harmer, C. J., Mackay, C. E., Reid, C. B., Cowen, P. J., & Goodwin, G. M. (2006). Antidepressant drug treatment modifies the neural processing of nonconscious threat cues. *Biological Psychiatry, 59,* 816–820. doi: 10.1016/j.biopsych.2005.10.015

Hayes, J. P., LaBar, K. S., McCarthy, G., Selgrade, E., Nasser, J., Dolcos, F., … Morey, R. A. (2011). Reduced hippocampal and amygdala activity predicts memory distortions for trauma reminders in combat-related PTSD. *Journal of Psychiatric Research, 45,* 660–669. doi: 10.1016/j.jpsychires.2010.1

Johansson, M., Mecklinger, A., & Treese, A. (2004). Recognition memory for emotional and neutral faces: An event-related potential study. *Journal of Cognitive Neuroscience, 16*, 1840–1853. doi: 10.1162/0898929042947883

Karl, A., Schaefer, M., Malta, L. S., Dörfel, D., Rohleder, N., & Werner, A. (2006). A meta-analysis of structural brain abnormalities in PTSD. *Neuroscience and Biobehavioral Reviews, 7,* 1004–1031. doi: 10.1016/j.neubiorev.2006.03

Keightley, M. L., Winocur, G., Graham, S. J., Mayberg, H. S., Hevenor, S. J., & Grady, C. L. (2003). An fMRI study investigating cognitive modulation of brain regions associated with emotional processing of visual stimuli. *Neuropsychologia*, *41*, 585–596. doi: 10.1016/S0028-3932(02)00199-9

Kensinger, E. A. (2004). Remembering emotional experiences: The contribution of valence and arousal. *Reviews in the Neurosciences, 15,* 241–251. doi: 10.1515/REVNEURO.2004.15.4.241

Kensinger, E. A., & Corkin, S. (2004). Two routes to emotional memory: Distinct neural processes for valence and arousal. *Proceedings of the National Academy of Sciences of the United States of America*, *101*, 3310–3315. doi: 10.1073/pnas.0306408101

Kensinger, E. A., & Schacter, D. L. (2006). Amygdala activity is associated with the successful encoding of item, but not source, information for positive and negative stimuli. *The Journal of Neuroscience*, *26*, 2564–2570. doi: 10.1523/JNEUROSCI.5241-05.2006

Kuo, J. R., Kaloupek, D. G., & Woodward, S. H. (2012). Amygdala volume in combat-exposed veterans with and without posttraumatic stress disorder: a cross-sectional study. *Archives of General Psychiatry*, *69*, 1080–1086. doi: 10.1001/archgenpsychiatry.2012.73

LaBar, K. S., & Phelps, E. A. (1998). Arousal mediated memory consolidation: role of the medial temporal lobe in humans. *Psychological Science*, *9*, 490–493. doi: 10.1111/1467-9280.00090

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1997). International affective picture system (IAPS): Technical manual and affective ratings. NIMH Center for the Study of Emotion and Attention.

Lanius, R. A., Bluhm, R. L., & Frewen, P. A. (2011). How understanding the neurobiology of complex post-traumatic stress disorder can inform clinical practice: A social cognitive and affective neuroscience approach. *Acta Psychiatrica Scandinavica, 124,* 331–348. doi: 10.1111/j.1600-0447.2011.01755.x

Lanius, R. A., Brewin, C. R., Bremner, J. D., Daniels, J. K., Friedman, M. J., Liberzon, I., … Vermetten, E. (2010a). Does neuroimaging research examining the pathophysiology of Posttraumatic Stress Disorder require medication-free patients? *Journal of Psychiatry and Neuroscience, 35,* 80–89. doi: 10.1503/jpn.090047

Lanius, R. A., Frewen, P. A., Girotti, M., Neufeld, R. W. J., Stevens, T. K., & Densmore, M. (2007). Neural correlates of trauma script-imagery in posttraumatic stress disorder with and without comorbid major depression: A functional MRI investigation. *Psychiatry Research: Neuroimaging, 155,* 45-56. doi: 10.1016/j.pscychresns.2006.11

Lanius, R. A., Vermetten, E., Loewenstein, R. J., Brand, B., Schmahl, C., Bremner, D., & Spiegel, D., (2010b). Emotion modulation in PTSD: Clinical and neurobiological evidence for a dissociative subtype. *The American Journal of Psychiatry, 167,* 640–647. doi: 10.1176/appi.ajp.2009.09081168

Lanius, R. A., Williamson, P. C., Bluhm, R. L., Densmore, M., Boksman, K., Neufeld, R. W., … Menon R. S. (2005). Functional connectivity of dissociative responses in PTSD: An fMRI investigation. *Biological Psychiatry, 15,* 873–884. doi: 10.1016/j.biopsych.2005.01.011

Lanius, R. A., Williamson, P. C., Boksman, K., Densmore, M., Gupta, M., Neufeld, R. W., … Menon, R. (2002). Brain activation during script-driven imagery induced dissociative

responses in PTSD: A functional MRI investigation. *Biological Psychiatry, 52,* 305–311. doi: 10.1016/S0006-3223(02)01367-7

Lanius, R. A., Williamson, P. C., Densmore, M., Boksman, K., Gupta, M., Neufeld, R. W., … Menon, R. (2001). Neural correlates of traumatic memories in posttraumatic stress disorder: A functional MRI investigation. *American Journal of Psychiatry, 158,* 1920–1922. doi: 10.1176/appi.ajp.158.11.1920

Lanius, R. A., Williamson, P. C., Densmore, M., Boksman, K., Neufeld, R. W., Gati, J. S., & Menon, R. S. (2004). The nature of traumatic memories: A 4.0 tesla fMRI functional connectivity analysis. *American Journal of Psychiatry, 161,* 36–44. doi:10.1176/appi.ajp.161.1.36

Lanius, R. A., Williamson, P. C., Hopper, J., Densmore, M., Boksman, K., Gupta M. A., … Menon, R. S. (2003). Recall of emotional states in posttraumatic stress disorder: A function MRI investigation. *Biological Psychiatry, 53,* 204–210. doi: 10.1016/S0006-3223(02)01466-X

Lecrubier, Y., Sheehan, D. V., Weiller, E., Amorim, P., Bonora, I., Sheehan, H.K. … Dunbar, G. C. (1997). The mini international neuropsychiatric interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. *European Psychiatry, 12,* 224-231. doi: 10.1016/S0924-9338(97)83296-8

Liang, K. C., Juler, R. G., & McGaugh, J. L. (1986). Modulating effects of posttraining epinephrine on memory: Involvement of the amygdala noradrenergic system. *Brain Research, 368,* 125–133. doi: /10.1016/0006-8993(86)91049-8

Lucassen, P. J., Pruessner, J., Sousa, N., Almeida, O. F., Van Dam, A. M., Rajkowska, G.,… Czéh, B. (2014). Neuropathology of stress. *Acta Neuropathologica, 127,* 109–135.

doi: 10.1007/s00401-013-1223-5

McDonough, J. R., & Kesner, R.P. (1971). Amnesia produced by brief electrical stimulation of the amygdala or dorsal hippocampus is cats. *Journal of Comparative and Physiological Psychology, 77,* 171–178. doi: 10.1037/h0031575

McGaugh, J. L. (2000). Memory: A century of consolidation. *Science, 287,* 248–251. doi: 10.1126/science.287.5451.248

McGaugh, J. L. (2002). Memory consolidation and the amygdala: A systems perspective. *Trends in Neuroscience, 25,* 456 – 461. doi: 10.1016/S0166-2236(02)02211-7

McGaugh, J. L. (2004). The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annual Review of Neuroscience, 27,* 1–28. doi: 10.1146/annurev.neuro.27.070203.144157

McGaugh, J. L., Cahill, L., & Roozendaal, B. (1996). Involvement of the amygdala in memory storage: Interaction with other brain systems. *Proceedings of the National Academy of Sciences of the United States of America, 93,* 13508–13514. Retrieved from: http://www.pnas.org/content/93/24/13508.full?tab=author-info

McKinnon, M. C., Yucel, K., Nazarov, A., & MacQueen, G. M. (2009). A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder. *Journal of Psychiatry and Neuroscience, 34,* 41–54. Retrieved from: http://ezproxy.lib.ryerson.ca/login?url=http://search.proquest.com.ezproxy.lib.ryerson.ca/docview/217314103?accountid=13631

Mickley Steinmetz, K. R. & Kensinger, E.A. (2009). The effects of valence and arousal on the neural activity leading to subsequent memory. *Psychophysiology, 46,* 1190–1199. doi: 10.1111/j.1469-8986.2009.00868.x

Mitra, R., Jadhav, S., McEwen, B. S., Vyas, A., & Chattarji, S. (2005). Stress duration modulates the spatiotemporal patterns of spine formation in the basolateral amygdala. *Proceedings of the National Academy of Sciences of the United States of America, 102*, 9371–9376. doi: 10.1073/pnas.0504011102

Morey, R. A., Dolcos, F., Petty, C. M., Cooper, D. A., Hayes, J. P., LaBar, K. S., & McCarthy, G. (2009). The role of trauma-related distractors on neural systems for working memory and emotion processing in posttraumatic stress disorder. *Journal of Psychiatric Research, 43*, 809–817. doi: 10.1016/j.jpsychires.2008.10.014

Morey, R. A., Gold, A. L., LaBar, K. S., Beall, S. K., Brown, V. M., Haswell, C. C., … Mid-Atlantic MIRECC Workgroup. (2012). Amygdala volume changes in posttraumatic stress disorder in a large case-controlled veterans group. *Archives of General Psychiatry, 11,* 1169–1178. doi: 10.1001/archgenpsychiatry.2012.50

Morgan, B., Terburg, D., Thornton, H. B., Stein, D. J., & van Honk, J. (2012). Paradoxical facilitationof working memory after basolateral amygdala damage. *PLoS One, 7,* e38116. doi: 10.1371/journal.pone.0038116

Murphy, S. E., Norbury, R., O'Sullivan, U., Cowen, P. J., & Harmer, C. J. (2009). Effect of a single dose of citalopram on amygdala response to emotional faces. *British Journal of Psychiatry, 194*, 535–540. doi: 10.1192/bjp.bp.108.056093

Onur, O. A., Walter, H., Schlaepfer, T. E., Rehme, A. K., Schmidt, C., Keysers, C. … Hurlemann, R. (2009). Noradrenergic enhancement of amygdala responses to fear. *Social Cognitive and Affective Neuroscience, 4*, 119–126. doi: 10.1093/scan/nsn049

Patel, R., Girard, T. A., & Green, R. E. A. (2012a). The influence of indirect and direct

emotional processing on memory for facial expressions. *Cognition & Emotion,* 26, 1143–1152. doi: 10.1080/02699931.2011.642848

Patel, R., Spreng, R. N., Shin, L. M., & Girard, T. A. (2012b). Neurocircuitry models of posttraumatic stress disorder and beyond: A meta-analysis of functional neuroimaging studies. *Neuroscience & Biobehavioral Reviews, 36*, 2130-2142. doi: 10.1016/j.neubiorev.2012.06

Paulus, M. P., & Stein, M. B. (2006). An insular view of anxiety. *Biological Psychiatry 60,* 383–387. doi: 10.1016/j.biopsych.2006.03.04

Pavlisa, G., Papa, J., Pavić, L., & Pavlisa, G. (2006). Bilateral MR volumetry of the amygdala in chronic PTSD patients. *Collegium Anthropologicum, 30,* 565-580. Retrieved from: http://ezproxy.lib.ryerson.ca/login?url=http://search.proquest.com.ezproxy.lib.ryerson.ca/docview/36593612?accountid=13631

Phelps, E. A., & Sharot, T. (2008). How (and why) emotion enhances the subjective sense of recollection. *Current Directions in Psychological Science, 17*, 147–152. doi: 10.1111/j.1467-8721.2008.0

Posner, J., Russell, J. A., & Peterson, B. S. (2005). The circumplex model of affect: An integrative approach to affective neuroscience, cognitive development, and psychopathology. *Development and Psychopathology, 17*, 715–734. doi: http://dx.doi.org/10.1017/S0954579405050340

Rauch, S. L., Shin, L. M., & Phelps, E. A. (2006). Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research—past, present, and future. *Biological Psychiatry, 60,* 376–382. doi: 10.1016/j.biopsych.2006.06.

Rauch, S. L., Shin, L. M., Whalen, P. J., & Pitman, R. K. (1998). Neuroimaging and the neuroanatomy of PTSD. *CNS Spectrums, 3* (Suppl. 2), 30–41.

Rauch, S. L., Whalen, P.J., Shin, L.M., McInerney, S. C., Macklin, M. L., Lasko, N.B., … Pitman, R. K. (2000). Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: A functional MRI study. *Biological Psychiatry, 47,* 769–776. doi: 10.1016/S0006-3223(00)00828-3

Resick, P. A., Monson, C. M., & Gutner, C. (2007). Psychosocial Treatments for PTSD. In: Friedman MJ, Keane TM, Resick PA, editors. *PTSD: Science and practice–A comprehensive handbook.* New York: Guilford Press; pp. 330–358.

Rogers, M. A., Yamasue, H., Abe, O., Yamada, H., Ohtani, T., Iwanami, A. … Kasai, K. (2009). Smaller amygdala volume and reduced anterior cingulate gray matter density associated with history of post-traumatic stress disorder. *Psychiatry Research, 174,* 210-216. doi: 10.1016/j.pscychresns.2009.0

Roozendaal, B., Hui, G. K., Hui, I. R., Berlau, D. J., McGaugh, J. L., & Weinberger, N. M. (2006). Basolateral amygdala noradrenergic activity mediates corticosterone-induced enhancement of auditory fear conditioning. *Neurobiology of Learning and Memory, 86,* 249–255. doi: 10.1016/j.nlm.2006.03.003

Roozendaal, B., Nguyen, B. T., Power, A., & McGaugh, J. L. (1999). Basolateral amygdala noradrenergic influence enables enhancement of memory consolidation induced by hippocampal glucocorticoid receptor activation. *Proceedings of the National Academy of Sciences of the United States of America, 96,* 11642–11647. Retrieved from: http://www.pnas.org/content/96/20/11642.long

Roozendaal, B., Portillo-Marquez, G., & McGaugh, J. L. (1996). Basolateral amygdala lesions block glucocorticoid-induced modulation of memory for spatial learning. *Behavioral Neuroscience, 110*, 1074–1083. doi: 10.1037/0735-7044.110.5.10

Roozendaal, B., & McGaugh, J. L. (1997). Basolateral amygdala lesions block the memory-enhancing effect of glucocorticoid administration in the dorsal hippocampus of rats. *European Journal of Neuroscience, 9*, 76–83. doi: 10.1111/j.1460-9568.1997.

Roozendaal, B., & McGaugh, J. L. (1997). Glucocorticoid receptor agonist and antagonist administration into the basolateral but not central amygdala modulates memory storage. *Neurobiology of Learning and Memory, 67*, 176–179. doi: 10.1006/nlme.1996.3765

Roozendaal, B., & McGaugh, J. L. (2011). Memory Modulation. *Behavioral Neuroscience, 125*, 797–824. doi: 10.1037/a0026187

Rosnow, R. J., & Rosenthal, R. (1989). Statistical procedures and the justification of knowledge in psychological science. *American Psychologist, 44*, 1276–1284. doi: 10.1037/0003-066X.44.10.1276

Rosnow, R. J., & Rosenthal, R. (1998). Focused tests of significance and effect size estimation in counseling psychology. *Journal of Counseling Psychology, 35*, 203–208. doi: 10.1037/0022-0167.35.2.203

Rowe, G., Hirsh, J. B., & Anderson, A. K. (2007). Positive affect increases the breadth of attentional selection. *Proceedings of the National Academy of Sciences of the United States of America, 104*, 383–388. doi: 10.1073/pnas.0605198104

Roy, A. K., Shehzad, Z., Margulies, D. S., Kelly, A. M., Uddin, L. Q., Gotimer, K., … Milham M. P. (2009). Functional connectivity of the human amygdala using resting state fMRI. *Neuroimage, 45,* 614–626. doi: 10.1016/j.neuroimage.2008.11.030

Russell, J. A. (1980). A circumplex model of affect. *Journal of Personality and Social Psychology, 39,* 1161–1178. doi: 10.1037/h0077714

Sharot, T., Delgado, M. R., & Phelps, E. A. (2004). How emotion enhances the feeling of remembering. *Nature Neuroscience, 7,* 1376–1380. doi: 10.1038/nn1353

Sharot, T., Verfaellie, M., & Yonelinas, A. (2007). How emotion strengthens the recollective experience: A time-dependent hippocampal process. *PLoS One, 2* (10), e1068. doi: 10.1371/journal.pone.0001068

Shin, L. M., Kosslyn, S. M., McNally, R. J., Alpert, N. M., Thompson, W. L., Rauch, S. L, … Pitman R. K. (1997). Visual imagery and perception in posttraumatic stress disorder: a positron emission tomographic investigation. *Archives of General Psychiatry, 54,* 233–241. Retrieved from: http://ezproxy.lib.ryerson.ca/login?url=http://search.proquest.com.ezproxy.lib.ryerson.ca/docview/206056231?accountid=13631

Shin, L. M., Whalen, P. J., Pitman, R. K., Bush, G., Macklin, M. L., Lasko, N. B., … Rauch, S. L. (2001). An fMRI study of anterior cingulate function in posttraumatic stress disorder. *Biological Psychiatry, 50*, 932–942. doi: 10.1016/S0006-3223(01)01215-X

Shin, L. M., Wright, C. I., Cannistraro, P. A., Wedig, M. M., McMullin, K., Martis, B., ... Rauch, S. L. (2005). A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. *Archives of General Psychiatry, 62,* 273–281. doi:10.1001/archpsyc.62.3.273

Shucard, J. L., Cox, J., Shucard, D. W., Fetter, H., Chung, C., Ramasamy, D., & Violanti, J. (2012). Symptoms of posttraumatic stress disorder and exposure to traumatic stressors are related to brain structural volumes and behavioral measures of affective stimulus processing in police officers. *Psychiatry Research, 204*, 25–31. doi: 10.1016/j.pscychresns.2012.0

Snodgrass, J. G. & Corwin, J. (1988). Pragmatics of measuring recognition memory: Application to dementia and amnesia. *Journal of Experimental Psychology, 117*, 34–50. doi: 10.1037/0096-3445.117.1.34

Spreng, R. N., Mar, R. A., & Kim, A. S. N. (2009). The common neural basis of autobiographical memory, prospection, navigation, theory of mind and the default mode: a quantitative meta-analysis. *Journal of Cognitive Neuroscience, 21,* 489–510. doi: 10.1162/jocn.2008.21029.

Sripada. R. K., King, A. P., Welsh, R. C., Garfinkel, S. N., Wang, X., Sripada, C. S., & Liberzon I. (2012). Neural dysregulation in posttraumatic stress disorder: evidence for disrupted equilibrium between salience and default mode brain networks. *Psychosomatic Medicine, 74*, 904–911. doi: 10.1097/PSY.0b013e318273bf33

St. Jacques, P. L., Kragel, P.A., & Rubin, D. C. (2013). Neural networks supporting autobiographical memory retrieval in posttraumatic stress disorder. *Cognitive, Affective, & Behavioral Neuroscience, 13*, 554–566. doi: 10.3758/s13415-013-0157-7

Talarico, J. M. & Rubin, D. C. (2003). Confidence, not consistency, characterizes flashbulb memories. *Psychological Science, 14.* 455–461. doi: 10.1111/1467-9280.02453

Thomaes, K., Dorrepaal, E., Draijer, N. P., de Ruiter, M. B., Elzinga, B. M., van Balkom, A. J., … Veltman, D. J. (2009). Increased activation of the left hippocampus region in

Complex PTSD during encoding and recognition of emotional words: a pilot study. *Psychiatry Research, 171*, 44–53. doi: 10.1016/j.pscychresns.2008.0

Tolin, D. F., & Foa, E. B. (2006). Sex differences in trauma and posttraumatic stress disorder: A quantitative review of 25 years of research. *Psychological Bulletin, 132*, 959–992. doi: 10.1037/0033-2909.132.6.959

Tomaz, C., Dickinson-Anson, H., & McGaugh, J. L. (1992). Basolateral amygdala lesions block diazepam-induced anterograde amnesia in an inhibitory avoidance task. *Proceedings of the National Academy of Sciences of the United States of America*, *89*, 3615–3619. Retrieved from: http://ezproxy.lib.ryerson.ca/login?url=http://search.proquest.com.ezproxy.lib.ryerson.ca/docview/72896933?accountid=13631

Van Ameringen, M., Mancini, C., Patterson, B., & Boyle, M. H. (2008). Post-traumatic stress disorder in Canada. *CNS Neuroscience & Therapeutics, 14*, 171-181. doi: 10.1111/j.1755-5949.2008.00049.x

Vyas, A., Pillai, A. G., & Chattarji, S. (2004). Recovery after chronic stress fails to reverse amygdaloid neuronal hypertrophy and enhanced anxiety-like behavior. *Neuroscience, 128*, 667–673. doi: 10.1016/j.neuroscience.2004.07.013

Weber, D. L., Clark, C. R., McFarlane, A. C., Moores, K. A., Morris, P., & Egan, G. F. (2005). Abnormal frontal and parietal activity during working memory updating in posttraumatic stress disorder. *Psychiatry Research, 140*, 27–44. doi: 10.1016/j.pscychresns.2005.07.003

Whalen, P. J., & Phelps, E. A. (Eds.). (2009). The human amygdala (pp. 265-288). New York: The Guilford Press.

Whalley, M. G., Kroes, M. C., Huntley, Z., Rugg, M. D., Davis, S. W., & Brewin CR. (2013). An fMRI investigation of posttraumatic flashbacks. *Brain & Cognition, 81,* 151–159. doi: 10.1016/j.bandc.2012.10.002

Woon, F. L., & Hedges, D. W. (2009). Amygdala volume in adults with posttraumatic stress disorder: a meta-analysis. *Journal of Neuropsychiatry and Clinical Neurosciences, 21*, 5-12. doi: 10.1176/appi.neuropsych.21.1.

Zwissler, B., Hauswald, A., Koessler, S., Ertl, V., Pfeiffer, A., Wöhrmann, C., … Kissler, J. (2012). Memory control in post-traumatic stress disorder: evidence from item method directed forgetting in civil war victims in Northern Uganda. *Psychological Medicine*, *42*, 1283–1291. doi: 10.1017/S0033291711002273