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Preferential recruitment of the basolateral amygdala during memory encoding of negative scenes in posttraumatic stress disorder

Ronak Patel [a,*], Todd A. Girard [b], Nicole Pukay-Martin [c], Candice Monson [b]

[a] Department of Clinical Health Psychology, College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada
[b] Department of Psychology, Ryerson University, Toronto, Ontario, Canada
[c] Trauma Recovery Center, Cincinnati VAMC – Ft. Thomas Division, Cincinnati, OH, United States

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ABSTRACT

Background: The vast majority of functional neuroimaging studies in posttraumatic stress disorder (PTSD) have examined the amygdala as a unitary structure. However, an emerging body of studies indicates that separable functions are subserved by discrete amygdala subregions. The basolateral subdivision (BLA), as compared with the centromedial amygdala (CMA), plays a unique role in learning and memory-based processes for threatening events, and alterations to the BLA have been implicated in the pathogenesis of PTSD. We assessed whether PTSD is associated with differential involvement of the BLA versus the CMA during successful encoding of emotionally charged events. *Methods:* Participants with PTSD ($n = 11$) and a trauma-exposed comparison (TEC) group ($n = 11$) viewed a series of photos that varied in valence (negative versus positive) and arousal (high versus low) while undergoing functional magnetic resonance imaging (fMRI). Subsequently, participants completed an old/new recognition memory test. *Results:* Using analytic methods based on probabilistic cytoarchitectonic mapping, PTSD was associated with greater activation of the BLA, as compared to the CMA, during successful encoding of negative scenes, a finding which was not observed in the TEC group. Moreover, this memory-related activity in the BLA independently predicted PTSD status. Contrary to hypotheses, there was no evidence of altered BLA activity during memory encoding of high arousing relative to low arousing scenes. *Conclusions:* Task-related brain activation in PTSD does not appear to be consistent across the entire amygdala. Importantly, memory-related processing of negative information in PTSD is associated with preferential recruitment of the BLA.

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1. Introduction

The current study interrogated the role of amygdala subregions during memory encoding of emotional events in posttraumatic stress disorder (PTSD). Despite evolving conceptualizations of PTSD, intrusive trauma recollections and other memory disturbances remain core features of the disorder (American Psychiatric Association, 2013), and the neural correlates underlying emotional memory in PTSD have garnered increasing attention (Brohawn, Offringa, Pfaff, Hughes, & Shin, 2010; Dickie, Brunet, Akerib, & Armony, 2008; Hayes et al., 2011). Animal studies have established that the amygdala plays a core role in modulating stress-related enhancement of conditioned fear responses (Gold & van Buskirk, 1978; Liang, Juler, & McGaugh, 1986; McGaugh, Cahill, & Roozendaal, 1996). Converging lines of evidence from lesion studies (Adolphs, Cahill, Schul, & Babinsky, 1997) and functional neuroimaging studies (Dolcos, LaBar, & Cabeza, 2005; Kensinger & Schacter, 2006) have also established that the amygdala is critically responsible for enhancing memory of emotional items in healthy humans (i.e., *emotional memory*). These findings support traditional neurocircuitry models of PTSD, which posit exaggerated amygdala activity as the neural basis underlying the intrusive nature of trauma-based recollections (Rauch, Shin, Whalen, & Pitman, 1998).

Functional neuroimaging studies of emotional memory in PTSD, however, have yielded mixed results. For example, consistent with the literature in healthy, non-clinical samples, Dickie et al. (2008) found that, in contrast to other regions (i.e., hippocampus and ventromedial prefrontal cortex), only amygdala activation at encoding

* Corresponding author at: Department of Clinical Health Psychology, College of Medicine, University of Manitoba, Health Sciences Centre, 771 Bannatyne Avenue, Winnipeg MB R3E 3N4, Canada.
E-mail address: rpatel4@exchange.hsc.mb.ca (R. Patel).

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predicted enhanced memory performance for fearful relative to neutral faces (Dickie et al., 2008), and that this activity was positively correlated with PTSD symptom severity. In a longitudinal follow-up study, the same group found PTSD symptom severity was positively associated with greater amygdala activity during successful encoding of negative stimuli (i.e., those stimuli that were later remembered), and that this came at the cost of decreasing activation toward neutral information (Dickie, Brunet, Akerib, & Armony, 2011). Although these results suggest that emotional memory-related activity in the amygdala plays a crucial role in the maintenance of PTSD symptoms, they are difficult to interpret in the absence of a comparison group. Other studies employing a trauma-exposed comparison group (TEC), have found PTSD-related *reductions* in amygdala activity during encoding of trauma-related photos that were subsequently remembered versus forgotten (Hayes et al., 2011). In contrast, Thomaes et al. (2009) failed to find differential amygdala activation in PTSD versus a TEC group during deep encoding of negative words that were later remembered.

Inconsistencies across these studies may stem from a number factors, including differences in experimental task, type of comparison group (TEC versus non-trauma exposure; Patel, Spreng, Shin, & Girard, 2012), and the nature of experimental stimuli. Although all have been raised as sources of variability in the literature, little attention has been given to the composition of the amygdala. In particular, the vast majority of neuroimaging studies have examined this structure as a single, homogeneous structure, potentially masking subregion-specific effects. Findings from animal studies demonstrate that the modulatory influences the amygdala has on fear conditioning are localized to the basolateral subdivision of the amygdala (BLA; McGaugh, 2002, 2004; Roozendaal et al., 2006). For instance, administration of a glucocorticoid agonist into the BLA, and not the centromedial amygdala (CMA), enhances retention in an inhibitory avoidance task, whereas pre-training infusion of a glucocorticoid antagonist into the BLA, but not the CMA, blocks enhanced retention (as measured by the latency to find a platform) in a water-maze escape task (Roozendaal & McGaugh, 1997).

Recent functional neuroimaging studies have harnessed probabilistic maps of post-mortem human amygdala subregions, derived from cytoarchitectonic mapping methods (Amunts et al., 2005), as a means to investigate the functions subserved by human amygdala subdivisions (Ball et al., 2007; Boll, Gamer, Gluth, Finsterbusch, & Büchel, 2013; Etkin, Prater, Schatzberg, Menon, & Greicius, 2009). Using this method, Onur et al. (2009) found that, compared with placebo administration of a norepinephrine reuptake inhibitor (i.e., reboxetine), healthy adults exhibited enhanced activity of the right BLA in response to fearful stimuli and decreased activation to neutral stimuli. The authors 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. They further suggested that disinhibited norepinephrine signaling could serve as a crucial etiological contributor to the onset and maintenance of PTSD by eliciting exaggerated BLA responses to negative information. Building on this foundation, we investigated whether PTSD, as compared to a TEC group, was associated with greater activity in the BLA versus the CMA, during successful memory encoding of emotional material. Although the amygdala is involved in processing a range of emotional information, it is most sensitive to negative and high arousing information (Whalen & Phelps, 2009). These two specific emotional properties appear to be most relevant to the etiological and clinical manifestations of trauma exposure in PTSD. Thus, we also examined the relations between emotional valence and arousal with subregional amygdala activation.

2. Method

2.1. Participants

Participants comprised individuals with a current diagnosis of PTSD ($n = 11$) and individuals who had been exposed to trauma, but who did not meet criteria for PTSD (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 established to have high inter-rater reliability and validity per independent reliability monitoring. Inter-rater reliability for the CAPS in our lab is excellent, ICC = 0.99.

Consistent with CAPS scoring and DSM-IV criteria, inclusion criterion for the PTSD group was 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. 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 within the past month. Additionally, participants did not have any history of neurological, learning, or psychotic disorders. 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 with the Mini International Neuropsychiatric Interview v. 6.0. ($n = 19$; Sheehan et al., 1997) or Structured Clinical Interview for DSM-IV ($n = 3$; First, Spitzer, Gibbon, & Williams, 2002) depending on study recruitment.

In the PTSD group, eight participants presented with a comorbid major depression ($n = 4$), anxiety ($n = 6$), or substance use disorder ($n = 2$). In terms of medication, six participants were not taking psychotropic medications at the time of testing, while the remaining five were taking prescribed anti-depressant medication. 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. 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 were free of comorbid diagnosis ($n = 9$); two presented with a comorbid anxiety disorder. A total of nine TEC participants were not taking medications, and one of the remaining two was prescribed an antidepressant. The TEC group did not differ from the PTSD group with respect to age, education, or sex (see Table 1). Depressive

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)
Time since trauma	*Mdn* = 10.00 (6.02)	*Mdn* = 12.00 (116.84[b])

Data shown: Mean (SD); *Mdn* = Median.
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; $p = .375$.
[b] Three participants in the PTSD group experienced their traumatic events greater than 15 years ago.
* $p < .01$ (statistical difference between groups, corrected for multiple comparisons using Bonferonni method).
** $p < .001$ (statistical difference between groups, corrected for multiple comparisons using Bonferonni method).

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