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Differential activity of subgenual cingulate and brainstem in panic disorder and PTSD

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ABSTRACT

Most functional neuroimaging studies of panic disorder (PD) have focused on the resting state, and have explored PD in relation to healthy controls rather than in relation to other anxiety disorders. Here, PD patients, posttraumatic stress disorder (PTSD) patients, and healthy control subjects were studied with functional magnetic resonance imaging utilizing an instructed fear conditioning paradigm incorporating both Threat and Safe conditions. Relative to PTSD and control subjects, PD patients demonstrated significantly less activation to the Threat condition and increased activity to the Safe condition in the subgenual cingulate, ventral striatum and extended amygdala, as well as in midbrain periaquaeductal grey, suggesting abnormal reactivity in this key region for fear expression. PTSD subjects failed to show the temporal pattern of activity decrease found in control subjects.

Panic disorder (PD) and posttraumatic stress disorder (PTSD) are anxiety disorders with evolving neurocircuitry models. Biological studies of anxiety disorders have focused on comparisons between patient groups and healthy controls, with only one neuroimaging study to date directly comparing PD and PTSD (Lucey et al., 1997). This resting state (single photon emission computed tomography, SPECT) study found significant cerebral blood flow (CBF) differences in obsessive compulsive disorder (OCD) and PTSD compared with PD and controls in bilateral superior frontal cortices and right caudate nuclei. However, to develop disorder-specific behavioral and pharmacological treatment approaches, knowledge of the differences in the underlying dysfunctional neurocircuitries in these disorders is required. Neurobehavioral and neurocircuitry models of PTSD suggest amygdalar hyperactivity and ventromedial prefrontal hypoactivity to external threat (Milad, Rauch, Pitman, & Quirk, 2006) whereas panic disorder appears to be marked by internally generated threat (Lissek et al., 2009) driven by dysfunctional ventromedial prefrontal (ACC), amygdalar and brainstem regions (Graeff & Del-Ben, 2008). Core components of panic disorder include autonomic signs like increased respiration, heart rate, and blood pressure which are modulated by key regions in the basal forebrain and the brainstem. The medial frontal cortical network (including Brodmann area 25) provides a major output to the hypothalamus and brain stem and contributes to this visceromotor system (Price, 1999). The ventral striatum, known for its central role in reward processing is implicated in coding emotional intensity and self-relatedness of a variety of stimuli, independent of their valence (Phan et al., 2004). The bed nucleus of the stria terminalis/extended amygdala may regulate fear perception and mediate anxiety (Davis & Shi, 1999).

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Table 1
Subject characteristics.

Primary diagnosis	Age	Gender	Secondary diagnosis
None	24	Male	None
None	28	Male	None
None	42	Female	None
None	33	Male	None
None	34	Male	None
None	31	Female	None
None	40	Female	None
None	49	Female	None
Panic disorder	35	Male	Generalized anxiety disorder (GAD), past Major depressive disorder (MDD)
Panic disorder	39	Male	Social phobia, agoraphobia
Panic disorder	50	Female	GAD, MDD
Panic disorder	24	Male	None
Panic disorder	34	Female	Past PTSD
Panic disorder	49	Female	GAD, specific phobia, personality disorders (avoidant, obsessive compulsive, and paranoid)
Panic disorder	28	Male	None
Panic disorder	36	Female	None
PTSD	45	Male	Mild MDD, GAD (subthreshold)
PTSD	37	Female	Social phobia, specific phobia, OCD, dysthymia
PTSD	36	Female	None
PTSD	38	Male	None
PTSD	41	Male	Binge eating disorder
PTSD	47	Female	Past EtOH dependence, past substance induced mania
PTSD	50	Female	Past MDD, past EtOH and substance dependence
PTSD	39	Male	GAD, MDD

Several studies have explored systemic pathophysiologic differences between PD and PTSD. PTSD and PD patients may have distinct profiles with respect to cortisol levels and hypothalamic-pituitary-adrenal (HPA) responsivity (Marshall et al., 2002); carbon dioxide sensitivity (Talesnik, Berzak, Ben-Zion, Kaplan, & Benjamin, 2007); polysomnography (Sheikh, Woodward, & Leskin, 2003); heart rate variability (Cohen et al., 2000), genetic contributions (Skre, Onstad, Torgersen, Lygren, & Kringlen, 1993); and acquisition of conditioned fear-potentiated startle to learned safety and danger cues (Lissek et al., 2009). A study utilizing eyeblink electromyography, heart rate, and skin conductance responses (SCR) before and during treatment with alprazolam in PD and PTSD found a decrease in response probability and a decrease in the SCR in PD, but not in PTSD (Shalev, Bloch, Peri, & Bonne, 1998). Since both diseases share key symptoms (e.g. panic attacks) and both are thought to be elicited by abnormal fear conditioning/fear learning (Gorman, Kent, Sullivan, & Coplan, 2000; Phelps & LeDoux, 2005) direct experimental comparison can help to differentiate the neurobiological underpinnings of both diseases and give direction to specific therapeutic targets.

In this study, we used functional magnetic resonance imaging (fMRI) to compare neural responses in PD patients relative to PTSD patients and healthy comparison subjects during an instructed fear paradigm consisting of a Threat and a Safe condition (Butler et al., 2007; Phelps et al., 2001). In this task, the association of a previously neutral stimulus with a possible aversive event is learned by means of a verbal instruction given before the start of the scan. Symbolically acquired fear results in physiological fear responses and functional neuroimaging data comparable to the responses to a conditioned stimulus and its extinction in classical fear condition-

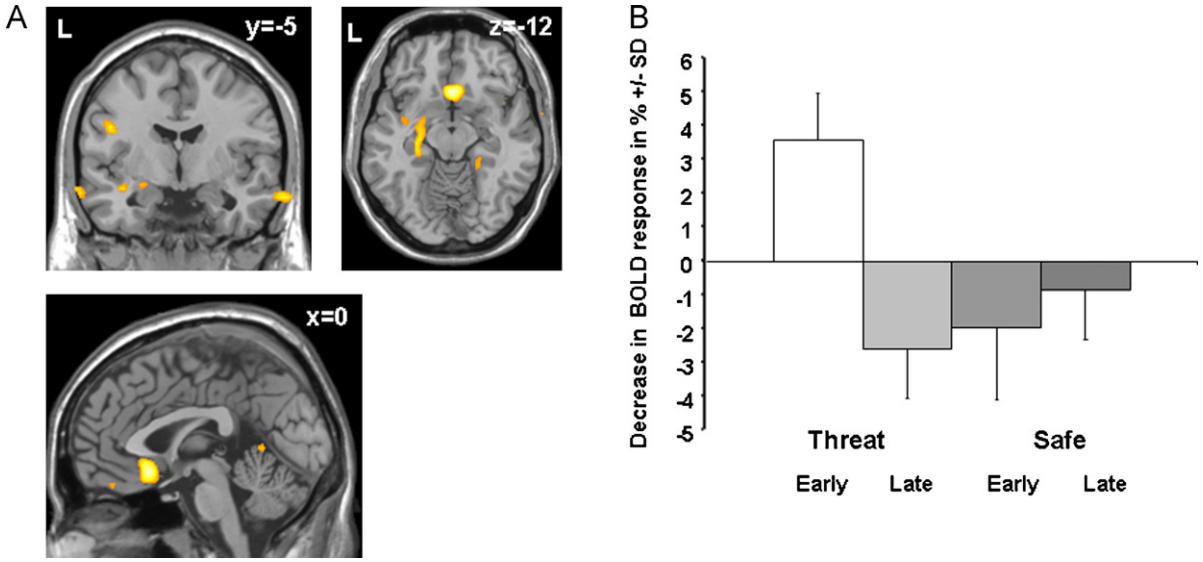

Fig. 1. (A) Coronal ($y = -5$), axial ($z = -12$), and sagittal ($x = 0$) sections showing increased amygdala activity and subgenual cingulate (Brodmann area 25) activity in early runs (parametric modeling of the Threat vs. Safe by Early vs. Late interaction) in Normal Control subjects ($p < 0.01$). (B) The bar plot shows the in BOLD response ± SD (%) at the point showing maximum activity for the Threat vs. Safe by Early vs. Late interaction in the amygdala (MNI [−21, 0, −12]). BOLD response is shown for Normal Controls, conditions [Threat, Safe], and study session [broken into Early and Late run] relative to a resting baseline.