

Neurocircuitry Models of Posttraumatic Stress Disorder and Extinction: Human Neuroimaging Research—Past, Present, and Future

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The prevailing neurocircuitry models of anxiety disorders have been amygdalocentric in form. The bases for such models have progressed from theoretical considerations, extrapolated from research in animals, to in vivo human imaging data. For example, one current model of posttraumatic stress disorder (PTSD) has been highly influenced by knowledge from rodent fear conditioning research. Given the phenomenological parallels between fear conditioning and the pathogenesis of PTSD, we have proposed that PTSD is characterized by exaggerated amygdala responses (subserving exaggerated acquisition of fear associations and expression of fear responses) and deficient frontal cortical function (mediating deficits in extinction and the capacity to suppress attention/response to trauma-related stimuli), as well as deficient hippocampal function (mediating deficits in appreciation of safe contexts and explicit learning/memory). Neuroimaging studies have yielded convergent findings in support of this model. However, to date, neuroimaging investigations of PTSD have not principally employed conditioning and extinction paradigms per se. The recent development of such imaging probes now sets the stage for directly testing hypotheses regarding the neural substrates of fear conditioning and extinction abnormalities in PTSD.

Key Words: Ventromedial prefrontal cortex, anterior cingulate cortex, orbitofrontal cortex, amygdala, hippocampus, magnetic resonance imaging, anxiety disorders, fear conditioning

Anxiety and fear are normal human emotional states that serve an adaptive function. The capacity to efficiently perceive, assess, learn about, and appropriately respond to cues and contexts that predict or signal danger is presumed to be critical to promoting survival across species. Anxiety disorders represent one category of psychiatric syndromes that are characterized by maladaptive anxiety symptoms that cause distress and impair function (American Psychiatric Association 1994). In particular, posttraumatic stress disorder (PTSD) is one of a few psychiatric conditions for which the etiology is defined. In PTSD, individuals develop a constellation of symptoms in the aftermath of a severe emotionally traumatic event. The cardinal triad of clinical features includes: re-experiencing phenomena (e.g., flashbacks, which can occur spontaneously or in response to reminders of the traumatic event), avoidance (e.g., avoiding situations that remind the individual of the traumatic event), and hyperarousal (e.g., exaggerated startle response). Given the phenomenology of PTSD, the fear-conditioning paradigm has been considered a valuable model for developing hypotheses about the pathophysiology of this disorder. Although the etiology of PTSD is defined in terms of the traumatic event, evolving models of pathogenesis take into account the potential interaction between the identified traumatic event (or events), past experiences, and intrinsic individual vulnerabilities.

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Neurocircuitry Model of PTSD

We have previously presented a neurocircuitry model of PTSD that emphasizes the role of the amygdala, as well as its interactions with the ventral/medial prefrontal cortex (vmPFC) and hippocampus (Rauch et al 1998). Briefly, this model hypothesizes hyperresponsivity within the amygdala to threat-related stimuli, with inadequate top-down governance over the amygdala by vmPFC (encompassing the rostral anterior cingulate cortex [rACC], medial prefrontal cortex [mPFC], subcallosal cortex [SC, including subgenual anterior cingulate cortex], and orbitofrontal cortex [OFC]) and the hippocampus. Amygdala hyperresponsivity mediates symptoms of hyperarousal and explains the indelible quality of the emotional memory for the traumatic event; inadequate influence by vmPFC underlies deficits of extinction as well as the capacity to suppress attention and response to trauma-related stimuli; and decreased hippocampal function underlies deficits in identifying safe contexts, as well as accompanying explicit memory difficulties (Bremner et al 1995). This model represents a final common pathophysiological pathway. Consequently, the pathogenesis of PTSD can be conceptualized as a fear-conditioning process that is superimposed over some diathesis, which could entail any combination of premorbid intrinsic amygdala hyperresponsivity, vmPFC deficiency, hippocampal deficiency, or exaggerated susceptibility to stress. Further, chronic PTSD might involve progressive deterioration of function (and structure) within this system.

Functional Neuroimaging Findings in PTSD

An initial positron emission tomography (PET) symptom provocation study of PTSD (Rauch et al 1996) used a script-driven imagery method for inducing symptoms. For the provoked versus control conditions, increased regional cerebral blood flow (rCBF) was found within the right amygdala and rACC, as well as other anterior paralimbic regions; decreases in rCBF were observed within the left inferior frontal region (Broca's area). Interpretations of this initial study, with regard to the pathophysiology of PTSD, were limited by the absence of a comparison group. A series of subsequent functional imaging studies were conducted where comparisons were made between

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subjects with PTSD and control subjects without PTSD, for contrasts between provoked versus control conditions, to test hypotheses about the pathophysiology of PTSD. Convergent results have suggested that when exposed to reminders of traumatic events (vs. control conditions), subjects with PTSD (vs. subjects without PTSD) exhibit greater responses within the amygdala (Shin et al 1997; Liberzon et al 1999; Pissiotta et al 2002; Hender et al 2003), attenuated responses within vmPFC areas (Bremner et al 1999a, 1999b; Shin et al 1999, 2004b; Lanius et al 2001; Lindauer et al 2004a), and exaggerated deactivation within other heteromodal frontal cortical regions (Shin et al 1997, 1999). These findings from symptom provocation studies were interpreted as providing initial support for the amygdalocentric neurocircuitry model of PTSD. However, it is important to note that replication across this full complement of experiments has been imperfect. This may be attributed to limited subject numbers with accompanying risks of type II error, as well as inconsistencies in experimental paradigms, and perhaps most importantly, heterogeneity in subject samples (e.g., Lanius et al 2001).

To test this model further, cognitive activation studies were used to measure the functional integrity at each node of the circuit: rACC, amygdala, and hippocampus. Using a functional magnetic resonance imaging (fMRI) probe of amygdala response (Whalen et al 1998b), Rauch et al (2000) found that in comparison with trauma-exposed subjects without PTSD, subjects with PTSD exhibited exaggerated amygdala responses to passively viewed masked fearful versus masked happy faces. The group \times condition contrast identified a locus in the right dorsal amygdala. In an analysis of data from each individual subject, it was shown that blood oxygenation level-dependent (BOLD) response within the amygdala to masked fearful versus masked happy faces correlated with an index of PTSD symptom severity (i.e., Clinician Administered PTSD Scale score), whereas BOLD response did not correlate with an index of depression severity (i.e., Beck Depression Inventory score). Further, an assessment of the main effect of condition across all subjects replicated the finding that this contrast illustrates recruitment of the amygdala in the absence of frontal cortical activation. Thus, these findings were interpreted as additional evidence of hyperresponsivity of the amygdala to threat-related stimuli in PTSD, even when relatively dissociated from the top-down influences of frontal cortex. A similar study from a different laboratory, using masked faces and an entirely independent sample, replicated the finding that the magnitude of right amygdala responses to masked fearful versus masked happy faces correlated with PTSD symptom severity (Armony et al 2005). Amygdala hyperresponsivity in PTSD has also been observed in response to nonmasked (i.e., overtly presented) fearful facial expressions (Shin et al 2005).

Using an fMRI Emotional Counting Stroop paradigm (Whalen et al 1998a), Shin et al (2001) found that in comparison with trauma-exposed subjects without PTSD, PTSD subjects exhibited attenuated recruitment of rACC in the context of a task that required suppressing processing of trauma-related information in favor of general negative information. This finding has now essentially been replicated in a cohort of female subjects (Bremner et al 2004) and indicates deficient function of rACC in PTSD in this context. In contrast, Bremner et al (2004) found no significant differences between PTSD and control subjects in dorsal anterior cingulate cortex (ACC) activation during a version of the Stroop Color-Word Test, underscoring the regional selectivity of the vmPFC functional abnormality.

Critical tests of the proposed neuroanatomical model of PTSD

will come from studies designed to assess the functional relationship between brain regions of interest in PTSD. Three recent studies have investigated the relationship between the medial prefrontal cortex and amygdala in this disorder. In a symptom provocation PET study, Shin et al (2004b) found that in the PTSD group, rCBF changes in medial frontal gyrus were significantly negatively correlated with rCBF changes in bilateral amygdala. Specifically, across subjects, as rCBF changes in medial frontal gyrus decreased, rCBF changes in amygdala increased. In addition, PTSD symptom severity was negatively correlated with medial frontal gyrus activity and positively correlated with amygdala activity. Shin et al (2005) reported similar findings in an fMRI study involving the presentation of fearful versus happy facial expressions in an independent sample of individuals with PTSD. In that study, amygdala responses to fearful versus happy faces were negatively correlated with medial prefrontal cortex responses in the PTSD group. Taken together, these findings suggest a reciprocal relationship between medial prefrontal cortex and amygdala function in PTSD, although the direction of causality remains undetermined. However, a recent PET study utilizing structural equation modeling found evidence for a positive relationship between the amygdala and anterior cingulate cortex (Gilboa et al 2004). Thus, additional research will be required to specify the direction of this relationship and to identify other important functional relationships among brain systems in PTSD.

A series of PET studies have utilized explicit learning paradigms as probes of hippocampal function in PTSD. Bremner et al (2003a, 2003b) have reported relatively diminished activation of hippocampus during the performance of a verbal paired associates task in abuse survivors with PTSD, as well as during encoding of a narrative paragraph. Likewise, using a word stem completion task, Shin et al (2004a) found diminished recruitment of hippocampus in firefighters with PTSD, relative to firefighters without PTSD. Together, these results also support the model of hippocampal dysfunction in PTSD. Interestingly, the findings of Shin et al (2004a) indicate elevated baseline hippocampal activity in PTSD, along with attenuated capacity for activation when called upon.

Structural and Neurochemical Imaging Findings in PTSD

To date, morphometric magnetic resonance imaging (MRI) studies of PTSD have focused on subtle between-group differences with respect to hippocampal volume. The possibility of reduced hippocampal volume and function is scientifically appealing, given that studies of chronic stress in animals have shown degenerative changes within the hippocampus associated with chronic exposure to glucocorticoids (Sapolsky et al 1990). In fact, an initial series of four studies showed smaller hippocampal volumes in adult subjects with PTSD versus groups of healthy control subjects (Bremner et al 1995, 1997; Gurvits et al 1996; Stein et al 1997) and/or trauma-exposed subjects without PTSD (Gurvits et al 1996). In some instances, investigators showed that these findings survived statistical control for alcohol abuse or years of education (Bremner et al 1995; Gurvits et al 1996) and that measures of hippocampal volume correlated with measures of verbal memory (Bremner et al 1995) or dissociative symptoms (Stein et al 1997), as well as indices of trauma exposure and PTSD symptom severity (Gurvits et al 1996). In addition, studies using magnetic resonance spectroscopy (MRS) have found significantly reduced relative concentrations of *N*-acetylaspartate (NAA) in hippocampus for PTSD versus control subjects (Schuff et

al 2001; Mohanakrishnan et al 2003), and some subsequent research has further replicated the finding of smaller hippocampal volumes in PTSD (Bremner et al 2003a; Shin et al 2004a; Lindauer et al 2004b). However, several subsequent MRI studies failed to show hippocampal volume differences when assessing children and adolescents with PTSD (DeBellis et al 1999; Carrion et al 2001), and two longitudinal studies failed to find reductions in hippocampal volumes over 6-month to 2-year follow-up periods (DeBellis et al 2001; Bonne et al 2001). An elegant monozygotic twin study, employing a twin design with discordance for trauma exposure, yielded findings suggesting that smaller hippocampal volume may represent a risk factor for developing PTSD if exposed to trauma (Gilbertson et al 2002), rather than a marker of pathophysiology per se. One study of adult burn patients indicated that smaller hippocampal volume was associated with traumatic exposure rather than PTSD (Winter and Irle 2004). Consequently, though initial MRI and MRS findings provided support for the hypothesis that PTSD is associated with smaller hippocampal volume, which, in turn, is associated with cognitive deficits and PTSD symptoms, subsequent results have complicated the picture with regard to the relationship between hippocampal volume and PTSD. Of note, a recent study indicated that chronic treatment with paroxetine was associated with improvement of PTSD symptom severity and declarative memory, as well as increased hippocampal volume (Vermetten et al 2003).

An initial cortical parcellation study (Rauch et al 2003) was recently performed and found that Vietnam combat-exposed nurses with PTSD versus without PTSD exhibited selectively reduced volumes in rACC and SC. In a voxel-based morphometry study, Yamasue et al (2003) found smaller gray matter volumes in the dorsal ACC in PTSD. Furthermore, these gray matter volumes were inversely related to PTSD symptom severity. Most recently, a study of PTSD subjects versus non-PTSD control subjects, using voxel-based morphometry as well as semiautomated volumetric analyses and probabilistic maps, replicated the finding of decreased gray matter within pregenual ACC (Corbo et al 2005); however, the results across methods indicated a difference in shape in that region rather than an absolute reduction in gray matter per se. These structural MRI findings resonate with a recent MRS study (DeBellis et al 2000) where maltreated children exhibited reduced NAA in the ACC.

Single-photon emission computed tomography (SPECT)/iomazenil findings of frontal cortical benzodiazepine binding abnormalities in PTSD (Bremner et al 2000) have thus far failed to replicate (Fujita et al 2004).

Summary of PTSD Neuroimaging Research to Date

Taken together, imaging data support the current neurocircuitry model of PTSD that emphasizes the functional relationship between a triad of brain structures: the amygdala, vmPFC, and hippocampus. When exposed to reminders of traumatic events, subjects appear to recruit anterior paralimbic regions and the amygdala, while exhibiting decreased activity within other heteromodal cortical areas. In comparison with control subjects, patients with PTSD exhibit vmPFC activation of diminished magnitude but exaggerated rCBF increases within other paralimbic regions, as well as the amygdala, and exaggerated decreases within widespread areas that are associated with higher cognitive functions. Cognitive activation experiments designed to probe the functional integrity within the nodes of this fear circuit have indicated hyperresponsivity within the amygdala to threat-re-

lated stimuli, diminished rACC activation during emotional Stroop tasks, and diminished activation of the hippocampus during various explicit encoding and retrieval tasks. To date, structural imaging studies have shown reduced volumes in rACC and SC, as well as hippocampus, without evidence of volumetric abnormality involving the amygdala. In parallel, MRS studies have found reduced NAA in ACC and hippocampus.

The Future of Neuroimaging Research in PTSD

Although current neurocircuitry models of PTSD are steeped in references to fear conditioning, thus far, neuroimaging studies of PTSD have yet to employ a full range of fear conditioning and extinction paradigms (Bremner et al 2005). Rather, as outlined above, neuroimaging of amygdala function in PTSD has involved reminders of the traumatic event or emotionally expressive face stimuli, rather than conditioned fear acquisition protocols. Similarly, neuroimaging studies of the vmPFC have utilized Stroop tasks rather than extinction training or retention paradigms, and studies of hippocampal function in PTSD have used explicit learning paradigms rather than ones designed to assess context effects. Therefore, we submit that the time is ripe for investigators to develop and employ neuroimaging paradigms that directly assess the neural substrates of fear conditioning and extinction in PTSD. As with prior cognitive activation studies of PTSD, it is important to first “validate” such functional imaging probes by demonstrating their effectiveness for mapping the mediating anatomy of these fear conditioning and extinction functions in healthy participants. Of note, in the psychophysiology laboratory setting, investigators have already shown that subjects with PTSD exhibit exaggerated de novo fear conditioning as well as deficits in fear extinction learning (e.g., Orr et al 2000). To our knowledge, thus far, only one published PET study of women with abuse-related PTSD versus healthy control subjects utilized a fear-conditioning and extinction-learning paradigm (Bremner et al 2005). In comparison with control subjects, during exposure to the conditioned stimulus, PTSD subjects exhibited greater amygdala activation during acquisition and decreased ACC function during extinction.

Neuroimaging Probes of Fear Conditioning and Extinction

Fear Conditioning and the Amygdala

Consistent with animal research (e.g., LeDoux 1996), several neuroimaging experiments of fear conditioning in healthy humans have likewise implicated the amygdala. Such studies have found significant correlation between rCBF changes in the right amygdala and electrodermal activity changes (Fredrikson et al 1995; Furmark et al 1997), as well as interregional correlations between amygdala and thalamus (Morris et al 1997). Several fMRI studies have also demonstrated amygdala activation during fear conditioning (LaBar et al 1998; Cheng et al 2003; Morris and Dolan 2004). This BOLD response in the amygdala to a reinforced conditioned stimulus (CS+) that is paired with a mild shock compared with an unreinforced conditioned stimulus (CS-) that is never paired with shock is correlated with electrodermal activity, indicating conditioned fear (LaBar et al 1998), and is most pronounced during the early trials of the fear conditioning, suggesting it attenuates over time (Buchel et al 1998; LaBar et al 1998). Similar results were reported by Büchel et al (1999) in a trace conditioning study, implicating hippocampus and amygdala. Knight et al (2004) have confirmed amygdala involvement during contingency changes in fear conditioning/

extinction. Finally, an fMRI paradigm has been developed using an aversive air puff (unconditioned stimulus [US]) to engage the amygdala during conditioning in pediatric subjects (Pine et al 2001). These various neuroimaging paradigms not only implicate the amygdala in human fear conditioning but also provide tools for future investigation of the neural substrates of conditioned fear acquisition in PTSD and other disorders.

Extinction and vmPFC

In addition to the established role of the rACC in the suppression of attention and response to emotionally valenced stimuli, recent research has focused on investigating the role of vmPFC in extinction processes. In rodents, it has been shown that extinction learning involves the medial prefrontal cortex (e.g., Morgan et al 1993) and that extinction recall in particular is mediated by infralimbic cortex (e.g., Milad and Quirk 2002; also see Quirk et al 2006 and Sotres-Bayon et al 2006, in this issue).

A recent fMRI study found a similar involvement of the vmPFC during the recall of extinction in humans (Phelps et al 2004). Activation of the amygdala and vmPFC, specifically a region of the rACC, was observed as participants acquired conditioned fear, extinguished conditioned fear in the same session, and recalled this extinction learning 24 hours later. Consistent with previous studies (LaBar et al 1998), activation of the amygdala to a CS+ compared with a CS– was correlated with the strength of the conditioned response during acquisition. Amygdala activation correlated with extinction success in the same session, although in this case a greater response to a CS–, compared with the CS+, indicated greater extinction, suggesting the amygdala may also play a role in early extinction training (see also Myers and Davis 2002; Knight et al 2004). During the recall of extinction after a 24-hour delay, activation of the vmPFC predicted extinction success and was correlated with amygdala activation (see also Gottfried and Dolan 2004), consistent with animal models indicating that the infralimbic cortex may act to inhibit the amygdala response during the recall of extinction (Milad and Quirk 2002).

Employing a novel extinction retention design (Milad et al 2005a) with similarities to that of Phelps et al (2004), Milad et al (2005b) conducted a morphometric MRI study in 14 healthy humans to test for correlations between regional cortical thickness and extinction recall. Using both region of interest (ROI)-based and pixelwise analyses, consistent with a priori hypotheses, the only locus within the entire brain that showed a reliable profile of association was located within vmPFC ($p < .001$; $r = .80$ – $.82$); cortical thickness was directly correlated with the magnitude of extinction recall. Further, this locus was mapped to within one resolution unit (~ 1 cm) of the peak voxel in the Phelps et al (2004) fMRI study of extinction recall.

Given that rACC, SC, and medial orbitofrontal cortex are hypothesized to be candidate human homologues of rodent infralimbic cortex (Ongur and Price 2000), these findings converge with the observation of decreased rACC and SC volumes in PTSD (Rauch et al 2003). Taken together, these data provide a hint at the potential link between brain structure, function, behavior, and psychopathology; smaller infralimbic/vmPFC volumes may mediate deficient extinction processes, leading to vulnerability to develop PTSD or other anxiety disorders.

Context and the Hippocampus

In rodents, the hippocampus has been shown to play a role in contextual fear conditioning, as well as context modulation of extinction retention (Corcoran and Maren 2004; Bouton 2004;

also see Bouton et al 2006, in this issue). Recent studies in humans have demonstrated context dependency of extinction retention, using peripheral physiological end points (e.g., skin conductance) (e.g., Milad et al 2005a; Vansteenwegen et al 2005). In addition, damage to the hippocampus in humans leads to an impairment in contextually mediated reinstatement of an extinguished fear (LaBar and Phelps 2005), consistent with animal models (Bouton 2004). Thus, these findings provide a foundation for developing analogous paradigms for use in conjunction with functional imaging. Neuroimaging research on context effects faces a unique challenge due to the fact that the imaging suite environment represents a powerful fixed context in its own right. Consequently, it is difficult to effectively manipulate context within an experimental imaging session. One approach to meet this challenge involves the use of virtual reality to achieve or simulate meaningful context manipulations during neuroimaging acquisition (Maguire et al 1998; Milad et al 2005a).

It is noteworthy that a careful review of the relevant animal literature highlights some discrepancy between the apparent role of the hippocampus in rodents and current theories about how limitations in hippocampal capacity would confer risk to develop anxiety disorders. To elaborate, given that the hippocampus plays a role in contextual fear conditioning (Sanders et al 2003; Rudy et al 2004), that pharmacological inactivation of the hippocampus facilitates the generalization of extinction across contexts and also interferes with renewal of conditioned fear following extinction (Corcoran and Maren 2001, 2004), and that damage to the hippocampus prevents the contextual reinstatement of conditioned fear (LaBar and Phelps 2005), one might hypothesize that diminished hippocampal function could be paradoxically protective by interfering with fear conditioning and promoting the generalization of extinction. Therefore, the model of PTSD that suggests hippocampal incapacity would confer risk by limiting the ability to appreciate safe contexts is, as yet, unfounded. It relies on the contention that the hippocampus may play an additional different role, with respect to context and fear, than that which has been commonly demonstrated in simple laboratory paradigms. Here, the findings of elevated baseline hippocampal activity by Shin et al (2004a) might be germane. To elaborate, elevated hippocampal activity in PTSD could impair generalization of extinction to novel contexts, though this is entirely speculative. Of course, there are also numerous other ways by which hippocampal dysfunction might influence PTSD and anxiety, such as via its role in explicit learning or in feedback regulation of the hypothalamic-pituitary-adrenal axis. Nonetheless, further research will be needed to clarify the role of the human hippocampus in contextual conditioning and in context modulation of extinction.

Implications for Cognitive and Behavioral Therapies

The implications of extinction research for behavior therapies are detailed in other articles within this special issue (see Davis et al 2006 and Hermans et al 2006, in this issue). Here, however, we wish to emphasize two points that are of particular relevance to neuroimaging. First, it remains to be determined to what degree cognitive therapies, which depend on conscious reappraisal of threatening stimuli or contexts, rely on the same neurocircuitry as behavior therapies that involve extinction processes (see Roffman et al 2005 for review). Functional magnetic resonance imaging studies have shown that conscious emotion regulation strategies, which are effective at diminishing fear responses and activation of the amygdala, rely on lateral prefrontal cortex (PFC)

regions, thought to underlie executive functions, that are phylogenetically more recent than the vmPFC regions known to be important for extinction (Ochsner et al 2002). However, a recent study examining emotion regulation of conditioned fear found that activation patterns in the vmPFC were similar when conditioned fear was diminished during extinction and emotion regulation (Phelps 2005). Furthermore, the activation pattern in this region during emotion regulation correlated with both the amygdala and lateral PFC, suggesting it might play a role in mediating the diminished amygdala response during conscious emotion regulation. These results suggest the intriguing possibility that cognitive strategies to regulate emotion may co-opt the mechanisms of extinction to diminish fear. Further research will be needed to determine precisely how the neural circuitry of behavioral and cognitive therapies might interact during treatment. Second, neuroimaging may provide information that can predict subsequent response to cognitive behavior therapies, which in turn could help to guide clinical management (Brody et al 1998). For instance, if cortical thickness or brain activation measures at specified loci within vmPFC can predict subsequent differential response to such therapies, this might lead to tests that can guide treatment planning in PTSD or other anxiety disorders.

Summary and Conclusions

Animal studies of fear conditioning and extinction have provided a foundation for neurocircuitry models of anxiety disorders in humans. Specifically, it has been hypothesized that PTSD is characterized by exaggerated amygdala responsivity and deficient top-down governance of the amygdala by vmPFC and hippocampus. Moreover, we have proposed that this regional pathophysiology in PTSD corresponds to exuberant acquisition of conditioned fear and exaggerated fear responses, as well as deficient extinction recall and an incapacity to appreciate safe contexts. In accord with this model, initial neuroimaging studies of PTSD provide evidence for exaggerated amygdala responses and attenuated vmPFC responses during exposure to reminders of the traumatic event. Further, in PTSD, specially designed cognitive activation paradigms have been used to demonstrate exaggerated amygdala responses to generally threatening stimuli as well as attenuated vmPFC and hippocampal responses during emotional Stroop and explicit memory tasks, respectively. Convergent with these functional imaging results, structural neuroimaging studies of PTSD have shown selectively reduced vmPFC and hippocampal volumes, while MRS studies have found reduced NAA in these same regions. Moreover, initial psychophysiological studies have indeed found exaggerated de novo fear conditioning and retarded extinction in PTSD versus comparison subjects. Nonetheless, further research is needed to more directly assess the prospective link between the clinical phenomena of PTSD, the observed abnormalities in fear conditioning and extinction, and their underlying neural substrates. Neuroimaging provides a uniquely powerful means to delineate the mediating anatomy of conditioning and extinction functions in humans and to quantitatively, as well as topographically, characterize the brain abnormalities associated with disturbances of these functions in PTSD. In particular, recent and ongoing studies promise to clarify the human neural substrates of extinction recall and its modulation by context. As neuroimaging paradigms are validated to test these functions, their application to the study of PTSD and other anxiety disorders will doubtless be illuminating. Finally, in addition to enriching our understanding of pathophys-

iology, this proposed line of inquiry may help to advance clinical care by clarifying the mechanisms of cognitive behavior therapies and predicting treatment outcomes (Milad et al 2006).

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- American Psychiatric Association (1994): *Diagnostic and Statistical Manual of Mental Disorders, 4th ed.* Washington, DC: American Psychiatric Association.
- Armory JL, Corbo V, Clement MH, Brunet A (2005): Amygdala response in patients with acute PTSD to masked and unmasked emotional facial expressions. *Am J Psychiatry* 162(10):1961–1963.
- Bonne O, Brandes D, Gilboa A, Gomori JM, Shenton ME, Pitman RK, et al (2001): Longitudinal MRI study of hippocampal volume in trauma survivors with PTSD. *Am J Psychiatry* 158:1248–1251.
- Bouton ME (2004): Context and behavioral processes in extinction. *Learn Mem* 11(5):485–494.
- Bouton ME, Westbrook RF, Corcoran KA, Maren S (2006): Contextual and temporal modulation of extinction: Behavioral and biological mechanisms. *Biol Psychiatry* 60:352–360.
- Bremner JD, Innis RB, Southwick SM, Staib L, Zoghbi S, Charney DS (2000): Decreased benzodiazepine receptor binding in prefrontal cortex in combat-related posttraumatic stress disorder. *Am J Psychiatry* 157(7):1120–1126.
- Bremner JD, Narayan M, Staib LH, Southwick SM, McGlashan T, Charney DS (1999a): Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. *Am J Psychiatry* 156:1787–1795.
- Bremner JD, Randall P, Scott TM, Bronen RA, Seibyl JP, Southwick SM, et al (1995): MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. *Am J Psychiatry* 152:973–981.
- Bremner JD, Randall P, Vermetten E, Staib L, Bronen RA, Mazure C, et al (1997): Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse—a preliminary report. *Biol Psychiatry* 41:23–32.
- Bremner JD, Staib LH, Kaloupek D, Southwick SM, Soufer R, Charney DS (1999b): Neural correlates of exposure to traumatic pictures and sound in vietnam combat veterans with and without posttraumatic stress disorder: A positron emission tomography study. *Biol Psychiatry* 45:806–816.
- Bremner JD, Vermetten E, Schmahl C, Vaccarino V, Vythilingam M, Afzal N, et al (2005): Positron emission tomographic imaging of neural correlates of a fear acquisition and extinction paradigm in women with childhood sexual-abuse-related post-traumatic stress disorder. *Psychol Med* 35(6):791–806.
- Bremner JD, Vermetten E, Vythilingam M, Afzal N, Schmahl C, Elzinga B, et al (2004): Neural correlates of the classic color and emotional Stroop in women with abuse-related posttraumatic stress disorder. *Biol Psychiatry* 55(6):612–620.
- Bremner JD, Vythilingam M, Vermetten E, Southwick SM, McGlashan T, Nazeer A, et al (2003a): MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. *Am J Psychiatry* 160:924–932.
- Bremner JD, Vythilingam M, Vermetten E, Southwick SM, McGlashan T, Staib LH, et al (2003b): Neural correlates of declarative memory for emotionally valenced words in women with posttraumatic stress disorder related to early childhood sexual abuse. *Biol Psychiatry* 53(10):879–889.
- Brody AL, Saxena S, Schwartz JM, Stoessel PW, Maidment K, Phelps ME, et al (1998): FDG-PET predictors of response to behavioral therapy versus

- pharmacotherapy in obsessive-compulsive disorder. *Psychiatry Res* 84:1–6.
- Büchel C, Dolan RJ, Armony JL, Friston KJ (1999): Amygdala-hippocampal involvement in human aversive trace conditioning revealed through event-related functional magnetic resonance imaging. *J Neurosci* 19:10869–10876.
- Büchel C, Morris J, Dolan RJ, Friston KJ (1998): Brain systems mediating aversive conditioning: An event-related fMRI study. *Neuron* 20:947–957.
- Carrion VG, Weems CF, Eliez S, Patwardhan A, Brown W, Ray RD, et al (2001): Attenuation of frontal asymmetry in pediatric posttraumatic stress disorder. *Biol Psychiatry* 50:943–951.
- Cheng DT, Knight DC, Smith CN, Stein EA, Helmstetter FJ (2003): Functional MRI of human amygdala activity during Pavlovian fear conditioning: Stimulus processing versus response expression. *Behav Neurosci* 117(1):3–10.
- Corbo V, Clement MH, Armony JL, Pruessner JC, Brunet A (2005): Size versus shape differences: Contrasting voxel-based and volumetric analyses of the anterior cingulate cortex in individuals with acute posttraumatic stress disorder. *Biol Psychiatry* 58(2):119–124.
- Corcoran KA, Maren S (2001): Hippocampal inactivation disrupts contextual retrieval of fear memory after extinction. *J Neurosci* 21(5):1720–1726.
- Corcoran KA, Maren S (2004): Factors regulating the effects of hippocampal inactivation on renewal of conditional fear after extinction. *Learn Mem* 11(5):598–603.
- Davis M, Ressler K, Rothbaum BO, Richardson R (2006): Effects of D-cycloserine on extinction: Translation from preclinical to clinical work. *Biol Psychiatry* 60:369–375.
- DeBellis MD, Hall J, Boring AM, Frustaci K, Moritz G (2001): A pilot longitudinal study of hippocampal volumes in pediatric maltreatment-related posttraumatic stress disorder. *Biol Psychiatry* 50:305–309.
- DeBellis MD, Keshavan MS, Clark DB, Casey BJ, Giedd JN, Boring AM, et al (1999): Developmental traumatology. Part II: Brain development. *Biol Psychiatry* 45:1271–1284.
- DeBellis MD, Keshavan MS, Spencer S, Hall J (2000): N-Acetylaspartate concentration in the anterior cingulate of maltreated children and adolescents with PTSD. *Am J Psychiatry* 157:1175–1177.
- Fredrikson M, Wik G, Fischer H, Andersson J (1995): Affective and attentive neural networks in humans: A PET study of Pavlovian conditioning. *Neuroreport* 7:97–101.
- Fujita M, Southwick SM, Denucci CC, Zoghbi SS, Dillon MS, Baldwin RM, et al (2004): Central type benzodiazepine receptors in Gulf War veterans with posttraumatic stress disorder. *Biol Psychiatry* 56(2):95–100.
- Furmark T, Fischer H, Wik G, Larsson M, Fredrikson M (1997): The amygdala and individual differences in fear conditioning. *Neuroreport* 8:3957–3960.
- Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, et al (2002): Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nat Neurosci* 5(11):1242–1247.
- Gilboa A, Shalev AY, Laor L, Lester H, Louzoun Y, Chisin R, et al (2004): Functional connectivity of the prefrontal cortex and the amygdala in posttraumatic stress disorder. *Biol Psychiatry* 55(3):263–272.
- Gottfried JA, Dolan RJ (2004): Human orbitofrontal cortex mediates extinction learning while accessing conditioned representations of value. *Nat Neurosci* 7(10):1144–1152.
- Gurvits TV, Shenton ME, Hokama H, Ohta H, Lasko NB, Gilbertson MW, et al (1996): Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. *Biol Psychiatry* 40:1091–1099.
- Hendler T, Rotshtein P, Yeshurun Y, Weizmann T, Kahn I, Ben-Bashat D, et al (2003): Sensing the invisible: Differential sensitivity of visual cortex and amygdala to traumatic context. *Neuroimage* 19(3):587–600.
- Hermans D, Craske MG, Mineka S, Lovibond PF (2006): Extinction in human fear conditioning. *Biol Psychiatry* 60:361–368.
- Knight DC, Smith CN, Cheng DT, Stein EA, Helmstetter FJ (2004): Amygdala and hippocampal activity during acquisition and extinction of human fear conditioning. *Cogn Affect Behav Neurosci* 4(3):317–325.
- LaBar KS, Gatenby C, Gore JC, LeDoux JE, Phelps EA (1998): Human amygdala activation during conditioned fear acquisition and extinction: A mixed-trial fMRI study. *Neuron* 20:937–945.
- LaBar KS, Phelps EA (2005): Reinstatement of conditioned fear in humans is context-dependent and impaired in amnesia. *Behav Neurosci* 119:677–686.
- Lanius RA, Williamson PC, Densmore M, Boksman K, Gupta MA, Neufeld RW, et al (2001): Neural correlates of traumatic memories in posttraumatic stress disorder: A functional MRI investigation. *Am J Psychiatry* 158:1920–1922.
- LeDoux JE (1996): *The Emotional Brain*. New York: Simon and Schuster.
- Liberzon I, Taylor SF, Amdur R, Jung TD, Chamberlain KR, Minoshima S, et al (1999): Brain activation in PTSD in response to trauma-related stimuli. *Biol Psychiatry* 45:817–826.
- Lindauer RJ, Booij J, Habraken JB, Uylings HB, Olff M, Carlier IV, et al (2004a): Cerebral blood flow changes during script-driven imagery in police officers with posttraumatic stress disorder. *Biol Psychiatry* 56(11):853–861.
- Lindauer RJ, Vlieger EJ, Jalink M, Olff M, Carlier IV, Majoie CB, et al (2004b): Smaller hippocampal volume in Dutch police officers with posttraumatic stress disorder. *Biol Psychiatry* 56(5):356–363.
- Maguire EA, Burgess N, Donnett JG, Frackowiak RS, Frith CD, O'Keefe J (1998): Knowing where and getting there: A human navigation network. *Science* 280(5365):921–924.
- Milad MR, Orr SP, Pitman RK, Rauch SL (2005a): Context modulation of memory for fear extinction in humans. *Psychophysiology* 42(4):456–464.
- Milad MR, Quinn BT, Pitman RK, Orr SP, Fischl B, Rauch SL (2005b): Thickness of ventromedial prefrontal cortex in humans is correlated with extinction memory. *Proc Natl Acad Sci U S A* 102(30):10706–10711.
- Milad MR, Quirk GJ (2002): Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature* 420:70–74.
- Milad MR, Rauch SL, Pitman RK, Quirk GJ (2006): Fear extinction in rats: Implications for human brain imaging and anxiety disorders. *Biol Psychol* 73(1):61–71.
- Mohanakrishnan Menon P, Nasrallah HA, Lyons JA, Scott MF, Liberto V (2003): Single-voxel proton MR spectroscopy of right versus left hippocampi in PTSD. *Psychiatry Res* 123(2):101–108.
- Morgan MA, Romanski LM, LeDoux JE (1993): Extinction of emotional learning: Contribution of medial prefrontal cortex. *Neurosci Lett* 163(1):109–113.
- Morris JS, Dolan RJ (2004): Dissociable amygdala and orbitofrontal responses during reversal fear conditioning. *Neuroimage* 22(1):372–380.
- Morris JS, Friston KJ, Dolan RJ (1997): Neural responses to salient visual stimuli. *Proc R Soc Lond B Biol Sci* 264:769–775.
- Myers KM, Davis M (2002): Behavioral and neural analysis of extinction. *Neuron* 36:567–584.
- Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD (2002): Rethinking feelings: An fMRI study of the cognitive regulation of emotion. *J Cogn Neurosci* 14:1215–1229.
- Ongur D, Price JL (2000): The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cereb Cortex* 10:206–219.
- Orr SP, Metzger LJ, Lasko NB, Macklin ML, Peri T, Pitman RK (2000): De novo conditioning in trauma-exposed individuals with and without posttraumatic stress disorder. *J Abnorm Psychol* 109:290–298.
- Phelps EA (2006): Emotion and cognition: insights from studies of the human amygdala. *Annu Rev Psychol* 57:27–53.
- Phelps EA, Delgado MR, Nearing KI, LeDoux JE (2004): Extinction learning in humans: Role of the amygdala and vmPFC. *Neuron* 43(6):897–905.
- Pine DS, Fyer A, Grun J, Phelps EA, Szasz PR, Koda V, et al (2001): Methods for developmental studies of fear conditioning circuitry. *Biol Psychiatry* 50:225–228.
- Pissiota A, Frans O, Fernandez M, von Knorring L, Fischer H, Fredrikson M (2002): Neurofunctional correlates of posttraumatic stress disorder: A PET symptom provocation study. *Eur Arch Psychiatry Clin Neurosci* 252(2):68–75.
- Rauch SL, Shin LM, Segal E, Pitman RK, Carson MA, Whalen PJ, et al (2003): Selectively reduced regional cortical volumes in posttraumatic stress disorder. *Neuroreport* 14(7):913–916.
- Rauch SL, Shin LM, Whalen PJ, Pitman RK (1998): Neuroimaging and the neuroanatomy of PTSD. *CNS Spectr* 3(suppl 2):30–41.
- Rauch SL, van der Kolk BA, Fisler RE, Alpert NM, Orr SP, Savage CR, et al (1996): A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. *Arch Gen Psychiatry* 53:380–387.
- Rauch SL, Whalen PJ, Shin LM, McInerney S, Macklin ML, Lasko NB, et al (2000): Exaggerated amygdala responses to masked facial stimuli in posttraumatic stress disorder: A functional MRI study. *Biol Psychiatry* 47:769–776.

- Roffman JL, Marci CD, Glick DM, Dougherty DD, Rauch SL (2005): Neuroimaging and the functional neuroanatomy of psychotherapy. *Psychol Med* 35(10):1385–1398.
- Rudy JW, Huff NC, Matus-Amat P (2004): Understanding contextual fear conditioning: Insights from a two-process model. *Neurosci Biobehav Rev* 28(7):675–685.
- Sanders MJ, Wiltgen BJ, Fanselow MS (2003): The place of the hippocampus in fear conditioning. *Eur J Pharmacol* 463(1–3):217–223.
- Sapolsky RM, Uno H, Rebert CS, Finch CE (1990): Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *J Neurosci* 10:2897–2902.
- Schuff N, Neylan TC, Lenoci MA, Du AT, Weiss DS, Marmar CR, et al (2001): Decreased hippocampal N-acetyl aspartate in the absence of atrophy in posttraumatic stress disorder. *Biol Psychiatry* 50:952–959.
- Shin LM, Kosslyn SM, McNally RJ, Alpert NM, Thompson WL, Rauch SL, et al (1997): Visual imagery and perception in posttraumatic stress disorder: A positron emission tomographic investigation. *Arch Gen Psychiatry* 54:233–241.
- Shin LM, McNally RJ, Kosslyn SM, Thompson WL, Rauch SL, Alpert NM, et al (1999): Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related posttraumatic stress disorder: A PET investigation. *Am J Psychiatry* 156:575–584.
- Shin LM, Orr SP, Carson MA, Rauch SL, Macklin ML, Lasko NB, et al (2004b): Regional cerebral blood flow in amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. *Arch Gen Psychiatry* 61:168–176.
- Shin LM, Shin PS, Heckers S, Krangel T, Macklin ML, Orr SP, et al (2004a): Explicit memory and hippocampal function in posttraumatic stress disorder. *Hippocampus* 14:292–300.
- Shin LM, Whalen PJ, McNerney SC, Macklin ML, Lasko NB, Orr SP, et al (2001): An fMRI study of anterior cingulate function in posttraumatic stress disorder. *Biol Psychiatry* 50:932–942.
- Shin LM, Wright CI, Cannistraro P, Wedig M, McMullin K, Martis B, et al (2005): An fMRI study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. *Arch Gen Psychiatry* 62:273–281.
- Sotres-Bayon F, Cain CK, LeDoux JE (2006): Brain mechanisms of fear extinction: Historical perspectives on the contribution of prefrontal cortex. *Biol Psychiatry* 60:329–336.
- Stein MB, Koverola C, Hanna C, Torchia MG, McClarty B (1997): Hippocampal volume in women victimized by childhood sexual abuse. *Psychol Med* 27:951–959.
- Vansteenwegen D, Hermans D, Vervliet B, Francken G, Beckers T, Baeyens F, et al (2005): Return of fear in human differential conditioning paradigm caused by a return to the original acquisition context. *Behav Res Ther* 43:323–336.
- Vermetten E, Vythilingam M, Southwick SM, Charney DS, Bremner JD (2003): Long-term treatment with paroxetine increases verbal declarative memory and hippocampal volume in posttraumatic stress disorder. *Biol Psychiatry* 54(7):693–702.
- Whalen PJ, Bush G, McNally RJ, Wilhelm S, McNerney SC, Jenike MA, et al (1998a): The Emotional Counting Stroop paradigm: A functional magnetic resonance imaging probe of the anterior cingulate affective division. *Biol Psychiatry* 44:1219–1228.
- Whalen PJ, Rauch SL, Etcoff NL, McNerney S, Lee MB, Jenike MA (1998b): Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *J Neurosci* 18:411–418.
- Winter H, Irle E (2004): Hippocampal volume in adult burn patients with and without posttraumatic stress disorder. *Am J Psychiatry* 161(12):2194–2200.
- Yamasue H, Kasai K, Iwanami A, Ohtani T, Yamada H, Abe O, et al (2003): Voxel-based analysis of MRI reveals anterior cingulate gray-matter volume reduction in posttraumatic stress disorder due to terrorism. *Proc Natl Acad Sci U S A* 100(15):9039–9043.