Neurobehavioral Mechanisms of Fear Generalization in PTSD

Lei Zhang

Duke University, Durham Veteran Affairs Medical Center

Introduction

Fear learning paradigms can provide important insight into the maintenance of the main symptoms of PTSD: re-experiencing, hyperarousal, and avoidance. In typical fear learning, danger is signaled by the similarity of current threat cues with previously encountered conditions that are predictive of aversive outcomes. In this way, fear learning allows an organism to display fear generalization by treating a stimulus that is highly similar to an already-learned threat as potentially harmful (Dunsmoor, Prince, Murty, Krage, & LaBar, 2011). Previous brain imaging research has implicated the amygdala, insula, cingulate gyrus, striatum, sensory cortex, and prefrontal cortex as critical regions for fear learning processes (Phelps and LeDoux, 2005).

Generalization of fear learning is adaptive in that it allows for an organism to quickly respond to novel stimuli based on previously acquired fear learning experience (Dusmoor, Mitroff, & LaBar, 2009). However, the transfer of fear, or overgeneralization of fear, to innocuous stimuli following a traumatic experience, as in PTSD, can lead to maladaptive behaviors and impair functioning in everyday life. For fear learning to be adaptive, organisms must express fear responses to novel threats while withholding fear responses to non-harmful stimuli (Dusmoor, Prince, Murty, Krage, & LaBar, 2011).

A previous study conducted by Dunsmoor and colleagues showed that healthy subjects conditioned to fear a moderately intense emotional face tended to generalize this fear to faces expressing greater emotional intensity (Dunsmoor, Prince, Murty, Krage, & LaBar, 2011). Functional magnetic resonance imaging (fMRI) revealed that activity in the amygdala and insula were correlated with individual variability of physiological arousal related to fear generalization

expression and that functional connectivity between the amygdala and fusiform face area increased when viewing a non-conditioned, high emotional intensity face; this increase was then positively correlated with trait anxiety (Dunsmoor, Prince, Murty, Krage, & LaBar, 2011). The aim of the present study is to examine fear generalization and the stress response of PTSD patients versus trauma-exposed control subjects using the same task as the one from the study conducted by Dunsmoor and colleagues. We will quantify the differences in brain activation between the PTSD and control groups in the cognitive processing regions (dorsolateral prefrontal cortex and lateral parietal cortex), stress modulation regions (amygdala, hippocampus, insula), and emotion processing regions (amygdala and ventrolateral prefrontal cortex).

Neuroimaging studies have revealed that patients with PTSD have structural and functional brain abnormalities. While looking at combat pictures within an fMRI scanner, patients with PTSD display greater activity in the amygdala compared to trauma-matched controls (Shin et al., 2005; Morey, Petty, Cooper, LaBar, & McCarthy, 2008). Studies on the structure of the brain have revealed differences in volume between the hippocampus, anterior, cingulate, and amygdala regions in PTSD patients versus trauma-matched controls (Gilbertson et al., 2002; Gross and Hen, 2004; May, Chen, Gilbertson, Shenton, & Pitman, 2004). These structural and functional differences in the brain may have a genetic basis, allowing for the use of imaging genetics to act as the link between gene and disease phenotype. Using biological plausibility, we aim to assay a targeted list of five genes in working memory and emotion processing. We will use this genotype information with the brain activation information from this present brain imaging study to analyze the interactions between genotype, brain activation, and PTSD severity within different brain regions to help identify genes associated with PTSD. (For the purposes of this paper, I will

only focus on the brain imaging component of this larger study, as I was only involved in this portion of the study).

Methods

Participants

160 subjects with PTSD and 160 trauma-matched controls without PTSD provided written informed consent to participate in the study. Subjects were all 18-65 years of age, fluent in English, capable of providing informed consent, free of implanted metal material for the fMRI scanner, unaffected by claustrophobia and were either OEF/OIF veterans, active military duty, or Guard/Reserve. Subjects were evaluated with the Clinician Administered PTSD Scale (CAPS). Subjects with significant neurological or psychotic disorders, learning disabilities, current/history of substance abuse, and significant medical conditions were excluded. Non-veteran/military subjects were not included.

Patient recruitment, evaluation, and data analysis were conducted at the Durham Veteran Affairs Medical Center. The non-PTSD subjects were matched with the PTSD group for trauma exposure and basic demographic variables such as age, gender, handedness, education, and race. Trauma exposure was determined using scores from the Combat Exposure Scale (Lund, Foy, Sipprelle, & Strachan, 1984) and the Traumatic Life Events Questionnaire (Kubany et al., 2000) that measure lifetime trauma exposure and severity for various traumatic events.

Task

This study utilized a fear generalization task involving a functional MRI machine, eye goggles, button box, and joystick. This study included an unpleasant stimulus – a mild electrical stimulus that was administered to the subject's dominant wrist by two electrodes, which were connected to the BIOPAC STM200 voltage stimulator. This electrical stimulation was adjusted before the experiment according to each subject's tolerance level. The stimulation was meant to be "annoying, but not painful."

To explore how PTSD contributes to the generalization of fear from one situation (e.g. combat) to another (e.g. everyday civilian life), this study was designed around Pavlovian fear conditioning that paired one stimulus with another. The unconditioned stimulus (US) was the mild electrical stimulation delivered to the subject's dominant wrist. Within the functional MRI scanner, subjects viewed a series of pictures of facial expressions from the Ekman series of emotional faces (Ekman and Friesen, 1976). These faces range from neutral to extremely fearful. The galvanic skin response was taken from the palm of the subject's non-dominant hand throughout the task as a dependent measure of physiological reactivity to the faces.

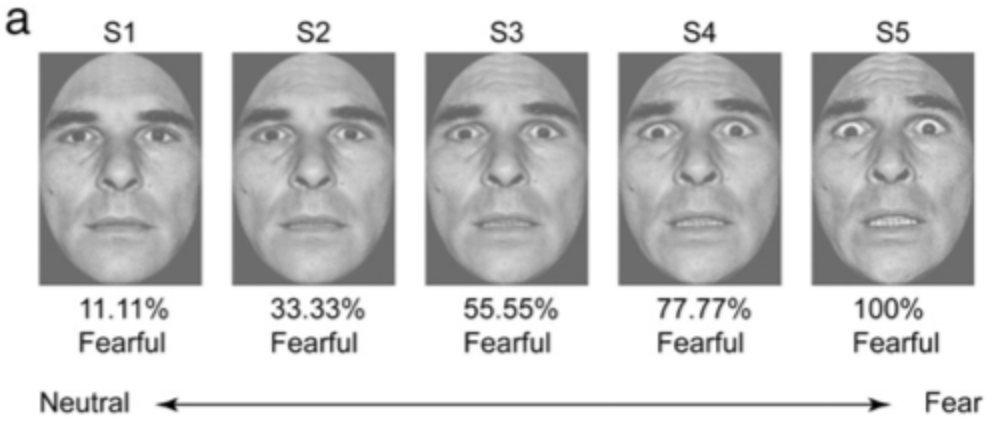

Figure 1: Range of faces subjects viewed within the fMRI scanner

The task within the scanner consisted of three phases: preconditioning/baseline (runs 1-3), fear conditioning/discrimination learning (runs 4-5), and fear generalization (runs 6-8). Initially, the subjects underwent runs 1-3 in which they viewed all the faces without any electrical stimulation. Subjects were asked to rate each face based on how much fear it was expressing. These runs were used to determine each subject's baseline level of responding to the stimuli. After the third run, subjects began the discrimination learning phase in which the moderately fearful face (CS+), labeled as S3 in figure 1, was paired with the electrical stimulation (US) while all other faces (CS-) were not paired with the stimulation. During this portion of the tasks, subjects rated the faces on their level of anticipation of receiving a shock. If the electrical stimulation accompanied the CS+, the stimulation was delivered after the rating. For these runs, the CS+ face was paired with the US on 8 out of 16 trials. After this discrimination learning phase, subjects underwent the fear generalization task in which the CS+ was paired with the US 3 times. The CS+ was shown to each subject while mixed in with the other faces, which were presented without the US.

After the task, subjects completed an extinction process by viewing the faces without any electrical stimulus (US) in order to ensure that the subjects would not generalize the CSs to situations outside the study setting. Each subject's skin response was also monitored to ensure that the subject did not react to the CS stimulus and that the US-CS relationship was extinguished.

Future Directions

Currently, we have not begun data analysis as we still need to run about 30 more PTSD patients and 30 more trauma-matched control patients through the fMRI scanner. Research assistants in the Morey lab will be continuing to run patients through this task through summer 2014 and into the fall semester if need be.

We anticipate that patients with PTSD will show an exaggerated fear response and increased rate of generalizing their fear of the moderately fearful face (S3) to faces that display a higher fearfulness expression due to the increased emotional salience and fear intensity of these two faces (S4 and S5). This is based on the tendency of PTSD patients to overgeneralize fear and the fact that even healthy subjects will generalize fear to stimuli of increased emotional intensity, as demonstrated by Dunsmoor and colleagues. This fear overgeneralization in PTSD patients will likely be expressed physiologically through their increased galvanic skin response to the S3, S4, and S5 faces compared to the controls and correlated with increased amygdala activity.

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