# Face Stroop in Post-Traumatic Stress Disorder: Emotional Interference

A thesis

submitted by

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## A BRIEF OVERVIEW

Posttraumatic stress disorder (PTSD) is a psychiatric disorder that can follow from a traumatic event. The disorder is characterized by unwanted emotional reactions and unwanted thoughts or memories regarding the traumatic event. Difficulty suppressing trauma- related thoughts or memories has been characterized as a key component of the pathology of PTSD (First et al., 1995; McNally, 1998). Given that patients with PTSD suffer from this sort of emotional interference, it has been hypothesized that this disorder involves an underlying pathology of emotional processing. To date, most researchers have studied emotional interference by utilizing stimuli that are directly related to the traumatic event. These studies have found an increase in response time (RT) during trauma-related emotional interference in PTSD groups, compared to control groups (for a review of the early emotional stroop literature see Williams et al., 1996; McNally, 1998). Additionally, during trauma-related emotional interference, some studies have found that participants with PTSD exhibit less activation in the rostral anterior cingulate (rACC), compared to healthy control subjects (Shin et al., 2001; Bremner et al., 2004). However, few previous experiments have utilized trauma-*unrelated* emotional stimuli to create emotional interference, and those that did reported no behavioral differences or rACC activation differences between PTSD and control groups (McNally et al., 1990; Foa et al., 1991; Cassiday et al., 1992; Shin et al., 2001).

There are two theoretical implications of this gap in the literature. The first possibility is that patients with PTSD exhibit hyporesponsivity in the rACC during emotional interference from only trauma-related stimuli. This would mean that in PTSD, trauma-related stimuli are special and may be processed differently than trauma-unrelated material. The second possibility is that patients with PTSD exhibit rACC hyporesponsivity to emotional interference from *any* sufficiently salient emotional stimuli. This would suggest that the previous study (Shin et al., 2001) did not find rACC

hyporesponsivity in the PTSD group for trauma-unrelated stimuli perhaps because the authors utilized insufficiently salient emotional stimuli.

To test this, we utilized the emotional Face Stroop, described below, which has been reported to create emotional interference in healthy subjects. Additionally, the Face Stroop elicits rACC activation (Etkin et al., 2006; Haas et al., 2006; Handwerger et al., unpublished manuscript). In the current experiment, we hypothesized that patients with PTSD would show relatively less rACC activation, compared to control participants, and that activation in the rACC in the PTSD group would be negatively correlated with PTSD symptom severity.

## SYMPTOMS AND EMOTIONAL INTERFERENCE

The symptoms of PTSD, which cause substantial disability, are thought to be associated with a dysfunction in normal emotional regulation. Successful regulation of strong emotions may involve dampening responses to emotional information so as to permit the performance of a given task (Gross, 1998). Both emotional and non-emotional information is streamed into the brain, while only crucial bits are allowed to be fully processed (Posner and Peterson, 1990). If this process breaks down, emotional information can interfere with a competing cognitive task, which is thought to happen as part of the pathology of PTSD (McNally et al., 1993; 1998).

In PTSD, this disrupted system is associated with biased attention to negatively valenced stimuli. For example, patients may be incapable of decreasing their arousal in the face of a stimulus that is reminiscent of the trauma. This may be related to an inability shift their attention away from the negative stimulus, or otherwise dampen the salience of the emotional content (McNally, 1998). To study biases in attention toward negative stimuli, researchers have implemented cognitive paradigms that assess

participants' ability to dampen the salience of highly valenced emotional information during the performance of a competing task.

One such paradigm is the Emotional Stroop (eStroop) (Williams, 1996), in which the classical color Stroop is altered to include words that are specifically tailored to a specific psychopathology. For example, patients with PTSD related to sexual assault may be asked to name the color of the word CUSHION in blue ink and later the word RAPE in red ink. Trauma specific words, compared to neutral words, have been reported to elicit an increase in response time, which is likely indicative of an emotional response (Foa et al., 1991; Cassiday et al., 1992). It is thought that the interference of the Emotional Stroop is directly related to an inability to suppress emotional information, which may be at the heart of the intrusive memories found in patients with PTSD. The semantic meaning of the word competes with naming the color of the word, which creates a delay in processing (McNally, 1993; 1998).

Most of the Emotional Stroop literature has relied on trauma-related words to produce a response time delay in PTSD. However, these studies have not reported a response time delay for trauma-unrelated emotional words (McNally et al., 1990; Foa et al., 1991; Cassiday et al., 1992). More recent Emotional Stroop studies have reported a relative decrease in the rACC blood oxygenation level dependent (BOLD) response for the PTSD group compared to the control group. However, these studies have only reported differential brain activation when using trauma related stimuli (Shin et al., 2001; Bremner et al., 2004).

## INTERFERENCE AND THE ANTERIOR CINGULATE CORTEX

In healthy participants, the response time delay observed in the Emotional Stroop is accompanied by activation of the rACC (Bremner et al., 2004; Mohanty et al., 2007). The rACC is a subdivision of the anterior cingulate cortex (ACC) and is thought to be

functionally distinct from the dorsal anterior cingulate cortex (dACC) (Vogt, 2005). Studies have found that the rACC responds more to emotional, or negatively valenced stimuli, compared to less negative or neutral stimuli (Whalen et al, 1998a; Teasdale et al., 1999; Mohanty et al., 2007), and may also play a role in emotional regulation (Urry et al., 2006). Meanwhile, the dACC is responsive typically during non-emotional tasks involving response selection, conflict monitoring, and error monitoring (Bush et al., 1998; Bush et al., 2000; Mohanty et al., 2007). The distinction between the rostral and dorsal areas of the cingulate has become relevant to the discussion of emotional interference and PTSD. The difficulty of regulating emotional information in PTSD is thought to be directly related to the functionality of the rACC and the dACC. Two paradigms that have elucidated the function of these cingulate areas are the Emotional Counting Stroop and the Counting Stroop.

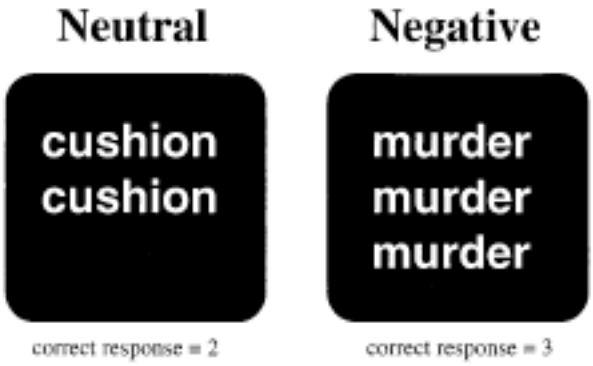



**Figure 1:** Emotional Counting Stroop stimuli. The box on the left is an example of a neutral stimulus, which the box on the right is an example of a negatively valenced stimulus. The correct response on the left is two, and three on the right (Figure from Whalen et al., 1998a).

The Emotional Counting Stroop

The Emotional Counting Stroop (ecStroop) is a paradigm that is similar to the emotional Stroop, and has been used to examine brain responses during emotional interference in healthy individuals (Whalen et al., 1998a). In this paradigm, the

participants were shown the same word repeated anywhere between one and four times. The word could be of neutral valence (cushion) or negative valence (murder). The task was to press a button corresponding to how many times the word appeared. A BOLD response was reported in the rACC during emotional vs. neutral conditions (Whalen et al., 1998a). This rACC activation was distinguishable from a more dorsal area of the cingulate, the dACC. This latter area exhibited an increased BOLD response during a non-emotional variant of the counting stroop (cStroop) task in the same subjects (Bush et al., 1998). Although there was a difference in BOLD response using the emotional vs. neutral contrast, there was no observed response time difference between the two conditions. Behavioral measures may not be as sensitive as BOLD response measures, and so the lack of a response time difference may be due to this lack of sensitivity (Whalen et al., 1998a). The ecStroop, a type of emotional stroop, highlights the role of the role of the rACC in inhibiting emotional information.

Etkin's Face Stroop:

Etkin and colleagues (2006) conducted a type of emotional stroop involving emotional faces (Face Stroop). The faces were either afraid or happy, and they had either the word *HAPPY* or *FEAR* superimposed over them. In the congruent condition, the superimposed word matched the face expression. In the incongruent condition, the superimposed word did not match the facial expression. In this way, Etkin's Face Stroop is similar to the current study (see below), however Etkin and colleagues analyzed their Face Stroop imaging data in a unique way. Each trial was defined by the trial that preceded it, focusing on 2 conditions. The authors chose to analyze two conditions that they called High Conflict Resolution, (or HCR, consisting of Incongruent trials preceded by Incongruent trials) and Low Conflict Resolution (or LCR, consisting of Incongruent

trials preceded by Congruent trials). See Chart 1 below for a representation of the two main conditions of interest from Etkin and colleagues.

| | **Current Trial** |
|---|---|
| **Previous Trial** | *Incongruent* |
| *Congruent* | Low Conflict Resolution (LCR) |
| *Incongruent* | High Conflict Resolution (HCR) |

**Chart 1**: Conditions used in Etkin et al., (2006).

Etkin et al., (2006) reported that, for the HCR condition compared to the LCR condition, the rACC increased in BOLD response. The authors hypothesized that the rACC may be involved in emotional conflict resolution, or that the rACC (as a part of the default network) was deactivating during the more difficult LCR condition (Etkin et al., 2006).

The circuitry involved in processing cognitive and emotional conflict has been implicated in the study of PTSD. Given that participants with PTSD have difficulty suppressing emotional content, it would make sense that PTSD would involve some disregulation of the rACC and dACC. In fact, there is considerable neuroimaging research to support a model of PTSD, focusing on the disregulation of the rACC, dACC, along with the amygdala. This is known as the neurocircuitry model of PTSD (Shin and Handwerger, 2009).

## Overview of the Neurocircuitry Model

The neurocircuitry model is related to the model for normal emotional regulation, which involves the dampening of emotional information in the amygdala via the medial prefrontal cortex (Urry et al., 2006), as well as animal models of fear conditioning and extinction (Milad and Quirk, 2002). In this model of PTSD, the dACC is thought to be

hyperresponsive. Meanwhile, the rACC is thought to be hyporesponsive, which may be related to a hyperresponsive amygdala (Shin and Handwerger, 2009). The most consistently reported finding in PTSD neuroimaging research is that the rACC is not as responsive as compared to a control group.

## Rostral Anterior Cingulate Cortex (rACC)

In healthy humans, acquisition and retention of this extinction memory is thought to be mediated by the ventromedial prefrontal cortex (vmPFC), possibly including the rACC (Phelps et al., 2004; Milad et al., 2007b). In addition, this brain area has been reported to respond to emotional stimuli, such as words, as seen above in Whalen et al., (1998a) (Teasdale et al., 1999; Mohanty et al., 2007). The rACC also responds to overtly presented afraid faces, compared to neutral faces (Kim et al., 2009). A similar study, where fear faces were contrasted to neutral house photos, has reported a negative correlation between rACC BOLD activation and STAI state scores (Bishop et al., 2004b).

The above findings of the rACC's responsivity to emotional stimuli, and inhibition of the amygdala is supported by subsequent face-stimuli paradigms. Here, using a fear vs. neutral contrast, the degree of inhibitive connectivity between rACC and the amygdala has been reported to negatively correlate with both neuroticism (Cremers et al., 2009) as well as STAI trait anxiety (Kim et al., 2009). Other research suggests that the rACC may functionally inhibit some nuclei of the amygdala, but not others (Roy et al., 2009). This makes sense given that, anatomically, it is thought that the vmPFC, and rACC send inhibitory projections to the amygdala (Vogt, 2005; Ongur and Price, 2000).

## rACC and PTSD

The most consistent finding with regard to PTSD is that the rACC is hyporesponsive (Newport and Nemeroff, 2000; Shin et al., 1999, 2004). This has been

reported in response to overt fear faces contrasted to both happy faces (Shin et al, 2005), and neutral faces (Williams et al., 2006). In addition, the rACC BOLD response in PTSD patients, produced for fearful vs. happy faces, has been found to positively correlate with that patient's symptom severity score (Shin et al., 2005). Patients with PTSD also exhibit this rACC hyporesponsivity during traumatic vs. neutral script driven imagery (Shin et al., 2004).

It has been reported that the degree of rACC responsivity during script driven imagery is negatively correlated with symptoms related to the re-experience of trauma (Hopper et al., 2007). In other words, less activation in the rACC is associated with more re-experiencing symptoms. BOLD activation in the rACC has also been reported to negatively correlate with PTSD symptom severity scores (Shin et al., 2001, 2005). Finally, pre-treatment activation of the rACC, in response to fear versus neutral faces, has been predictive of treatment response in PTSD (Felmingham et al., 2007).

## Dorsal Anterior Cingulate Cortex (dACC)

The dACC is thought to be involved in response conflict (MacDonald et al., 2000), as well as deciding on the lesser of two negative outcomes (Blair et al., 2006). The dACC also increases in activation during emotion regulation, especially increasing the feeling of a negative emotion (Urry et al., 2009). However, it is important to note that the dACC responds to decreasing a negative emotion as well (Urry et al., 2009). With regard to fear conditioning, dACC activation positively correlates with the expression of conditioned fear responses in humans (Milad et al., 2007a).

## dACC and PTSD

More recently, some evidence has indicated that the dACC may be hyperresponsive in PTSD (Bryant et al., 2005; Felmingham et al., 2009). In fact, some

studies suggest that patients with PTSD preferentially activate the dACC during tasks that normally activate the rACC (Shin et al., 2001).

This was the case when the ecStroop was used to study rACC responses in PTSD patients. In doing so, it was found that combat exposed patients with PTSD failed to activate their rACC, while combat exposed participants *without* PTSD were capable of activating their rACC (Shin et al., 2001), similar to the healthy subjects in Whalen, et al. (1998). It was noted by the researchers that, although the PTSD patients failed to elicit a BOLD response in the rACC, activation was present in the dACC (Shin, 2001). These results suggest that participants with PTSD preferentially utilize the dACC for tasks that normally utilize the rACC

In a similar study, the cStroop was administered to a PTSD population, and a non-significant trend was reported ($p<0.08$) toward an increase in dACC BOLD activation for the PTSD group, compared to Trauma Exposed Control Participants (TENP) (Shin et al., 2007). These results support the hypothesis that dACC responsivity may be increased in PTSD.

A recent fear conditioning study showed that PTSD participants exhibited elevated dACC BOLD responses during extinction recall (Milad et al., 2009). In addition, there was a non-significant trend toward a negative correlation between dACC BOLD response and percent extinction retention (Milad et al., 2009).

Recently, in a twin study, combat veterans with PTSD as well as their asymptomatic, combat unexposed co-twins exhibited greater resting glucose metabolic rates in the dACC, relative to non-PTSD veterans and their identical co-twins. Furthermore, dACC metabolism in the combat unexposed twins was correlated with the symptom severity score of their combat-exposed co-twins (Shin et al., 2009). These results suggest that an elevated resting metabolism in the dACC could predispose an individual to develop PTSD (Shin et al., 2009).

## The Amygdala

The amygdala is an area of the brain that has consistently been demonstrated to respond to emotional stimuli (LeDoux, 2000; Bishop et al., 2004a). This is especially true for fear specific facial cues (Whalen et al., 1998b, 2004), along with fear faces in general (Rauch et al., 2000). In healthy participants, it has been reported that amygdala responsivity to fearful faces, versus neutral stimuli, has been reported to positively correlate with STAI State ratings (Bishop et al., 2004a). In addition, BOLD responsivity in the amygdala positively correlates with the expression of a conditioned fear response, as measured by skin conductance response (Phelps et al., 2004), and is also elevated during fear conditioning (Milad et al., 2007b).

Although the amygdala has been characterized as the center of fear and negative emotion, it is also involved in positive affect and reward (Baxter and Murray, 2002; Murray, 2007). For instance, the amygdala is not only involved in conditioning; it is also involved in extinction (Milad et al., 2007). It's possible that the amygdala influences reward via connections with the medial prefrontal cortex (mPFC) and thalamus (Baxter and Murray, 2002) or via the substantia innominata and the extended amygdala connection with the nucleus accumbens (Alheid and Heimer 1988).

## Amygdala in PTSD

It is currently thought that the amygdala is hyperresponsive in PTSD (Rauch et al., 2000, 2006; Shin et al., 2005; Williams et al., 2006; Bryant et al., 2008). In fact, the outcome of PTSD treatment can be predicted on the basis of pretreatment amygdala BOLD responses to fear versus happy faces (Felmingham et al., 2007; Bryant et al., 2008). Symptom severity scores in PTSD patients have been found to correlate negatively with BOLD responses in the amygdala for overt fear faces, compared to

happy faces (Armony et al., 2005). Meanwhile amygdala BOLD responses for masked fear faces vs. happy faces correlate positively with symptom severity (Rauch et al., 2000; Armony et al., 2005). It has also been reported that participants with PTSD exhibited greater amygdala BOLD responsivity during extinction learning, and an impaired recall of the extinction memory (Milad et al., 2009).

## THE CURRENT STUDY

It has been established that patients with PTSD exhibit some difficulty processing stimuli that are associated with their traumatic event. Indeed, all of the early emotional Stroop experiments reported that PTSD groups (compared to control groups) exhibit an increase in interference for trauma-related words (for a review of the early emotional stroop literature see Williams et al., 1996; McNally, 1998).

We recognize that two recent studies have examined emotional interference from trauma-unrelated emotional information (Vythilingam et al., 2007; Pannu-Hayes et al., 2009) while only one of them examined BOLD responsivity (Pannu-Hayes et al., 2009). Vythilingam and colleagues reported that participants with PTSD, compared to control participants, exhibited significantly greater emotional interference for trauma-unrelated emotional stimuli compared to neutral stimuli. This study suggests that participants with PTSD can exhibit increased emotional interference to trauma-unrelated material. However, the authors did not examine BOLD responsivity and cannot comment on our hypothesized rACC hyporesponsivity in the PTSD group during trauma-unrelated emotional interference (Vythilingam et al., 2007). Similar to Vythilingam et al., (2007), Pannu-Hayes and colleagues (2009) used emotional photos as a distracter, rather than relying on classical semantic Stroop interference as in the present study. Although the authors included an imaging component, they did not report a group difference in rACC BOLD response for trauma-unrelated emotional stimuli, compared to neutral stimuli

(Pannu-Hayes et al., 2009). Given these past results, it is currently unclear whether patients with PTSD exhibit rACC BOLD hyporesponsivity during emotional interference from trauma-unrelated stimuli; we aimed to examine this with the Face Stroop.

We predicted that the Face Stroop would allow us to examine all three regions of interest in PTSD: the rACC, dACC and amygdala. This paradigm consisted of overt faces with words superimposed over the facial expressions, which were presented to the subjects in a functional magnetic resonance imaging (fMRI) scanner. The faces were either happy or afraid, and the words read either *happy*, *afraid*, or a non-word baseline (*XXXXX*). In the congruent condition, the superimposed word matched the face expression. In the incongruent condition, the superimposed word did not match the facial expression. Using a button box, subjects were asked to indicate the expression of the face, responding as quickly and as accurately as possible.


**Figure 2:** Seen above are face stimuli used in the Face Stroop. Subjects are asked to identify the emotion being expressed by the face. All faces were either happy or afraid. The face on the left is an example of a congruent trial, where the word matches the facial expression. The face in the center is an example of an incongruent trial, where the word does not match the facial expression. The face on the right is an example of a baseline trial, with a string of letters (XXXXX) over the face.

One potential advantage of this paradigm is that we could potentially explore the functional connectivity between the dACC and rACC. Another advantage of this task is

the use of face stimuli, which produce amygdala responses (Morris et al., 1996) not seen in the ecStroop (Whalen et al., 1998a). Amygdala responses to fear vs. happy faces may be modulated by the rACC, both of which are areas of interest (Bishop et al., 2004a).

The Face Stroop has been tested in healthy control subjects and was found to produce greater response times on the Incongruent versus Congruent trials (Handwerger et al., unpublished manuscript). Additionally, the Face Stroop has been reported to elicit a BOLD response in the rACC and the dACC in healthy control subjects (Handwerger et al., unpublished manuscript). Given these preliminary results, it can be inferred that the Face Stroop is producing the emotional interference that it was hypothesized to do.

Behavioral Hypotheses

Many (McNally et al., 1990; Cassiday et al., 1992; Kaspi et al., 1995), but not all (Foa et al., 1991) emotional Stroop studies have reported significantly slower response times overall in the PTSD group, compared to healthy groups. Based on these previous results, we hypothesized that patients with PTSD, compared to trauma exposed control participants, would have slower response times and more error rates, as evidenced by a main effect of group.

As measured by response time, previous evidence has suggested that the Incongruent stroop condition is more difficult than the Congruent stroop condition (Stroop, 1935). Additionally, emotional Face Stroop paradigms that are similar to our current study have suggested that the incongruent condition is more difficult than the congruent condition (Meeren et al., 2005; Etkin et al., 2006; Haas et al., 2006). We therefore hypothesized that the responses to the Incongruent condition would be significantly slower and contain more errors, compared to the Congruent condition.

Previous emotional stroop experiments have reported that patients with PTSD would answer more slowly and commit more errors during trauma-relevant stimuli, compared to control (McNally et al., 1990; Foa et al., 1991; Cassiday et al., 1992). However, this is not typically the case for trauma-unrelated, emotional words (Foa et al., 1991). Given that we are not using trauma-relevant stimuli in our task, we did not hypothesize an interaction between group and condition.

rACC Hypotheses

It was predicted that the TENP group would exhibit greater BOLD responsivity in the rACC during the Incongruent (I) condition compared to the Congruent (C) condition (i.e., the IvC contrast). Previous research has suggested that the rACC may have an inverse relationship with the amygdala (Bremner et al., 2005; Kim et al., 2003a; Pezawas et al., 2005); we predicted a similar relationship to be found in the current study in both groups. Previous research has suggested that high trait anxiety is related to a decrease in structural integrity between the rACC and amygdala (Kim et al., 2009). Based on these results, we hypothesized that the PTSD group would exhibit less functional connectivity between the rACC and amygdala.

For the PTSD group, IvC BOLD activation in the rACC was predicted to negatively correlate with current scores on the Clinician Administered PTSD Scale (CAPS) (Blake et al., 1997).

dACC Hypotheses

The PTSD group was predicted to display greater IvC BOLD responsivity in the dACC, relative to the TENP group. In addition, it was hypothesized that the dACC activation in the IvC contrast would positively correlate with current CAPS scores in the PTSD group. For both groups, also it was hypothesized that the dACC activation in the

IvC contrast would positively correlate with the difference in response times between Incongruent and Congruent trials. The BOLD responses in the dACC (IvC) of both groups were predicted to inversely correlate with the BOLD responses in the rACC. We also hypothesized that the dACC of both groups would positively correlate with the amygdala, and that this correlation would be greater in the PTSD group.

| Region of Interest | Greater in | Correlate |
|---|---|---|
| rACC | TENP group | 1) Negatively with amygdala in both groups, but greater correlation in the TENP group.<br>2) Negatively with dACC in both groups, but greater correlation in the TENP group.<br>3) PTSD group: Negatively with CAPS |
| dACC | PTSD group | 1) Positively with amygdala in both groups, but stronger correlation in the PTSD group<br>2) Positively with IvC response time in both groups<br>3) PTSD group: Positively with CAPS<br>4) Negatively correlate with the dACC, but greater correlation in the TENP group |

**Chart 2:** Overview of the neuroimaging hypotheses for the IvC Contrast.

Amygdala Hypotheses

We hypothesized that the amygdala would increase in BOLD responsivity for Fear (F) faces, compared to Happy (H) faces (i.e., the FvH Contrast). This was hypothesized because of the similarity of the FvH contrast to the overt faces paradigm (Morris et al., 1996). Furthermore, we hypothesized that the FvH amygdala response would be greater in participants with PTSD. For the PTSD group only, amygdala activation in the FvH contrast was also hypothesized to positively correlate with current CAPS scores.

Etkin Analysis:

Although it was not a part of our original analysis, we tried to replicate the findings of Etkin and colleagues (2006), who analyzed their Face Stroop results in a unique manner. The authors used a High Conflict Resolution (HCR) condition, compared to a Low Conflict Resolution (LCR) condition. These conditions are discussed in detail greater detail in the *Methods* section.

Etkin and colleagues reported a relative increase in BOLD response in the rACC for the HCR condition compared to the LCR condition (HCRvLCR contrast). For the same contrast, the authors reported a relative decrease in the dorsomedial prefrontal cortex (dmPFC) and amygdala Etkin et al., 2006). We expected to replicate these results in our TENP group.

We predicted that the HCRvLCR contrast would produce a greater rACC BOLD response in the TENP group compared to the PTSD group. Previous evidence has suggested that dmPFC activation is hyporesponsive in PTSD, along with rACC activation (Shin et al., 2005). We therefore hypothesized that the LCRvHCR dmPFC activation would be greater in the TENP group. Furthermore, we hypothesized that the increase in LCRvHCR amygdala activation would be greater in the PTSD group.

## METHODS

Subjects:

We recruited 42 right-handed trauma-exposed participants in total. Of these, 21 participants had current PTSD. Two subjects were removed due to excessive movement during the scan, one subject stopped the scan before the Face Stroop began, and one subject failed to respond to an adequate number of trials. In our final analysis, we included 17 subjects in the PTSD group (14 female, 3 male).

The other 21 participants met criterion A for PTSD, but did not meet criteria for either a full diagnosis of PTSD or any other Axis I disorders. Two of these subjects were excluded due to a button box malfunction, and one subject was excluded due to excessive errors. In our final analysis, we included 18 subjects in the TENP group (13 female, 5 male).

PTSD diagnoses were made using the Clinician Administered PTSD scale (CAPS) (Blake et al., 1997). All other diagnoses were made using the Structured Clinical Interview for the DSM-IV Axis I Disorders (First et al., 1995).

Exclusionary criteria included complicating major medical conditions, such as stroke, seizure disorder, major head trauma, pregnancy (as determined by a urine HCG pregnancy test prior to the fMRI scan). Any MRI contraindications, such as metal implants, pacemakers, or non-removable piercings were considered exclusionary. No participants were using any psychotropic medications or had a history of drug/alcohol abuse in the last 6 months.

Psychometric Measurements

Subjects were administered the Spielberger State-Trait Anxiety Inventory (STAI) (Spielberger, 1983); Edinburgh Handedness survey (Oldfield, 1971), NEO Five Factor

Personality Inventory (Costa & McCrae, 1985); the Beck Depression Inventory (BDI) (Beck & Steer, 1987); and the Beck Anxiety Inventory (BAI) (Beck & Steer, 1990).

Stimuli and Procedures

Both PTSD and TENP participants completed the Face Stroop task. The stimuli consisted of black and white photos of 5 male and 5 female faces, each modeling one happy and one afraid expression (Ekman & Friesen, 1976). Every face was superimposed with either the word *happy*, *afraid*, or a string of Xs (*XXXXX*). Face stimuli in the congruent condition were superimposed with a word matching the facial expression. Meanwhile, face stimuli in the incongruent condition were superimposed with a word that did not match the face expression. Face stimuli for the non-word baseline condition were superimposed with a string of Xs. This was included as an intermediate baseline, between the congruent condition and the null (fixation cross) baseline, but was not included in the final analysis. Examples of all conditions can be seen in Figure 2, above.

The Optseq program (http://surfer.nmr.mgh.harvard.edu/optseq/) was used to jitter the presentation timing. Each face was presented for 1300 milliseconds, with a 700 milliseconds inter-stimulus interval, in a pseudorandom order such that the facial expressions of one identity were never presented in succession. Across each of the runs, each fearful and happy face was presented equally for a total of 180 stimuli per run. Interleaved within the facial stimuli were 28 white fixation crosses (null trials), which were presented for either 1300 milliseconds, or 3300 milliseconds. Subjects completed four runs (6 minutes and 40 seconds/run) of this task, but for the proposed analysis, only the first two runs were used in data analysis to avoid decrements in amygdala and ACC activation that occur with extended practice (Bush et al., 1998; Britton et al., 2008).

The facial stimuli were displayed using MacStim Carbon 3.2.1 and projected via a Sharp Notevision6 (XG-NV6XU) LCD projector (Osaka, Japan). Subjects were asked to use a button box to respond as to whether the presented face was happy or afraid, with one button assigned to each emotion. The assignment of the buttons was counterbalanced across subjects. After scanning, participants were asked to assess the valence (negative – positive: -3 to +3) and arousal (low – high: 0 to 6) of the experimental stimuli. They were then debriefed about the purpose of the research and allowed to ask any questions about the experiment at that time.

Behavioral Analyses

Response times were averaged across correct trials within each condition for analysis. Two separate 2 (Group: PTSD, TENP) x 2 (Condition: Incongruent, Congruent) analyses of variance (ANOVA) were used to analyze response time and error rate data.

In an effort to replicate findings from Etkin and colleagues (2006), the data were also analyzed using a 2 (group) x 2(Condition: High Conflict Resolution, Low Conflict Resolution) ANOVA.

Image Acquisition:

All of the fMRI data were collected on Mass General Hospital's Charlestown campus, in the Martinos Center. A Symphony/Sonata 1.5 Tesla (T) whole body high-speed imaging device equipped for echo planar imaging (Siemens Medical Systems, Iselin, NJ) with a 3-axis gradient head coil was used to collect fMRI data. Head movement was restricted using pads and foam cushions. In order to optimize field homogeneity, an automated scout image was acquired and shimming procedures completed (Reese, Davis, & Weisskoff, 1995). Subsequently, two high-resolution 3D MPRAGE sequences (TR/TE/Flip angle=2730ms/3.39ms/7°), with 1.33 mm in plane

resolution and 1mm slice thickness, were collected for both spatial normalization and for positioning the slice prescription of subsequent scans. Individual functional data were registered using a T1-weighted (TR/TE/=8sec/39ms) and T2-weighted (TR/TE/Flip angle=5640ms/95ms/150°) sequences. We acquired EPI (functional) MRI images (Kwong et al., 1992) using gradient echo T2-weighted sequence (TR/TE/Flip angle=2sec/40ms/90°).

To allow longitudinal magnetization to reach equilibrium, four images were acquired and discarded before the start of each functional scan. The T1, T2, and functional images were collected in the same plane (22 coronal slices perpendicular to the ac-pc line) with the same slice thickness (7mm, 1 mm gap; voxel size 3.1x3.1x7.0), interleaved excitation order, and foot-to-head phase encoding.

Data Analysis

We performed all fMRI statistical analyses, including preprocessing with SPM 2.0 package (Wellcome Department of Cognitive Neurology, London, UK; Friston, Frith, Liddle and Frackowiak, 1991). Images were slice time corrected, realigned and co-registered. Anatomy images and functional images were then normalized to an averaged brain template and smoothed with a 7mm Gaussian kernel.

In SPM 2.0, voxelwise Incongruent vs. Congruent, Fear vs. Happy and HCR vs. LCR contrast images were created for each participant. Data from the first two runs per participant were included in this analysis. All trials involving errors of omission and commission were removed. At each voxel, the data were fitted into a linear statistical model by the method of least squares. The BOLD responses were modeled as events convolved with the hemodynamic response function. Hypotheses were tested as contrasts in which linear compounds of the model parameters were evaluated using *t* statistics, which were then transformed into *z*-scores.

Random effects analyses were then performed to assess the difference between groups. The statistical parametric maps resulting from the random effects analyses were inspected for activations in the rACC, dACC, and the amygdala, which were the a priori regions of interest. The dACC was defined as the portion of the ACC superior to the corpus callosum, between *y* =0 mm and *y* =+30 mm, and z<+48mm (Bush et al., 2002). The rACC is defined as the portion of ACC immediately anterior to the dACC, with z >0 mm. The superior, anterior, and lateral boundaries of rostral ACC were determined by the cingulate sulcus, which can be visualized on structural images (Shin et al., 2001).

The 3D MPRAGE images were spatially normalized, and smoothed within SPM 2.0 (7-mm full width at half maximum [FWHM]). ROI analyses were focused on the dACC, rACC and amygdala (as mentioned above), using a significance threshold of *p* <.001 (one-tailed), uncorrected for multiple comparisons. Any activation observed outside of the predefined ROIs were subject to the stricter threshold of *p*<.00001.

Contrasts:

The main contrast of interest in this study was comparing the Incongruent condition to the Congruent condition (IvC). We also conducted the IvC contrast with only fear faces (FIvFC) and only happy faces (HIvHC). The FIvFC and HIvHC analyses were conducted to control for any potential modulation of the IvC contrast by different emotional stimuli. We also analyzed the data by contrasting the Fear trials against the Happy trials, in a contrast (FvH) that was similar to a paradigm where subjects viewed emotional faces (Morris et al., 1996).

A separate analysis was conducted to reproduce the analysis done by Etkin and colleagues (Etkin et al., 2006). This was done by separating incongruent trials based on the condition type that preceded them, which produced two new conditions. The first condition consisted of Incongruent trials preceded by Congruent trials (Low Conflict

Resolution or LCR) while the second condition consisted of Incongruent trials preceded by Incongruent trials (High Conflict Resolution or HCR). From the IvC contrasts, the FvH contrast and Etkin's HCRvLCR contrast, between subject comparisons were made, examining the differences in activation between the PTSD group and TENP group.

Voxelwise whole brain correlations:

We took individual IvC or FIvFC subject maps and ran voxel-wise whole brain correlations by running simple regressions within SPM2. We entered in continuous variables as covariates and explored the hypothesis that these variables predicted voxel values within the contrast. We used this method to explore the relationship between the IvC contrast and CAPS score, extracted rACC values, and extracted dACC values. We also explored the relationship between FIvFC contrast and CAPS score.

## RESULTS

Our primary interest was to examine the effect of emotional interference by using the Face Stroop in trauma-exposed participants both with and without PTSD. To that end, we examined the behavioral and imaging differences between the incongruent condition and the congruent condition. The results of the IvC, and FvH contrast are discussed in the section below. We also attempted to replicate the findings of Etkin et al., (2006).

PSYCHOMETRIC DIFFERENCES:

| VARIABLE | TENP MEAN | PTSD MEAN | SIGNIFICANCE |
|---|---|---|---|
| AGE | 27.06 | 29.88 | *P*=NS |
| BMI | 23.43 | 25.44 | *P*=NS |
| BDI* | 1.27 | 13.12 | *P*<0.001 |
| BAI* | 2.11 | 15.00 | *P*<0.001 |
| STAI-S* | 27.61 | 39.53 | *P*<0.001 |
| STAI-T* | 30.44 | 47.75 | *P*<0.001 |
| NEO-N* | 25.17 | 38.44 | *P*<0.001 |
| NEO-E | 41.50 | 38.75 | *P*=NS |
| NEO-O | 43.67 | 44.63 | *P*=NS |
| NEO-A* | 47.67 | 43.94 | *P*<0.009 |
| NEO-C | 44.83 | 46.69 | *P*=NS |

**Chart 3**: Psychometric differences between the groups. Note: Asterisk (*) denotes a significant difference between the groups.

BEHAVIORAL DATA:

Error Rates:

We analyzed error rates first by only examining errors of *commission*, using a 2 (Group: PTSD, TENP) x 2 (Condition: Incongruent, Congruent) ANOVA. As expected, there was a main effect of condition $F(1, 33)=21.203$, $p<0.001$), with higher error rates during the Incongruent condition (mean = 2.572%), compared to Congruent condition (mean = 0.836%). There was no main effect of group $F(1,33)=0.201$, $p=.657$ nor was there an interaction between group and condition $F(1,33)=1.014$, $p=.321$.

We repeated this analysis while including errors of omission along with errors of commission and report similar results. There was a main effect of condition $F(1,33)=34.655$, $p<0.001$, with higher error rates during the Incongruent condition (mean = 7.795%) compared to Congruent condition (mean = 3.848%). There was no main effect of group $F(1,33)=2.673$, $p=0.112$, nor was there an interaction between group and condition $F(1,33)=0.298$, $p=0.298$. In tandem with our imaging analyses (see below), we also isolated the Fear and Happy trials and ran two separate ANOVAs for each.

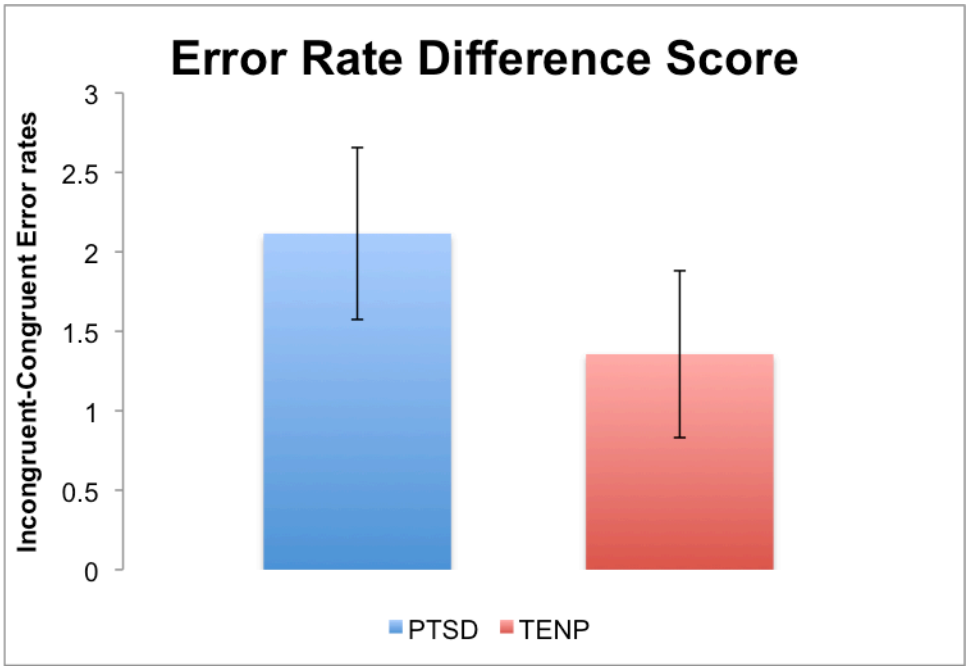



**Figure 3:** Error rates for the Incongruent vs. Congruent trials PTSD and TENP groups. There was no significant difference in IvC Error rates between the groups.

FIvFC Error analysis

For the IvC analyses with only Fear trials (FIvFC), we ran a 2 (Group: PTSD, TENP) x 2 (Condition: Fear Incongruent, Fear Congruent) ANOVA. As with the IvC ANOVA, there was a main effect of condition $F(1, 33)=19.931$, $p<0.001$, with higher ERs in the FI condition (mean=2.987) compared to the FC condition (mean=0.659). There

was no main effect of group $F(1,33)<0.001$, $p=0.983$ or an interaction between group and condition $F(1,33)=0.237$, $p=0.630$.

HIvHC Error analysis

For the IvC analyses with only Happy trials (HIvHC), we ran one 2 (Group: PTSD, TENP) x 2 (Condition: Happy Incongruent, Happy Congruent) ANOVA. As with previous analyses, there was a main effect of condition $F(1,33)=8.289$, $p=0.007$, with higher ERs in the HI condition (mean=2.156) compared to the HC condition (mean=0.659). There was no main effect of group $F(1,33)=0.505$, $p=0.482$ or an interaction between group and condition $F(1,33)=1.620$, $p=0.212$.

Response times:

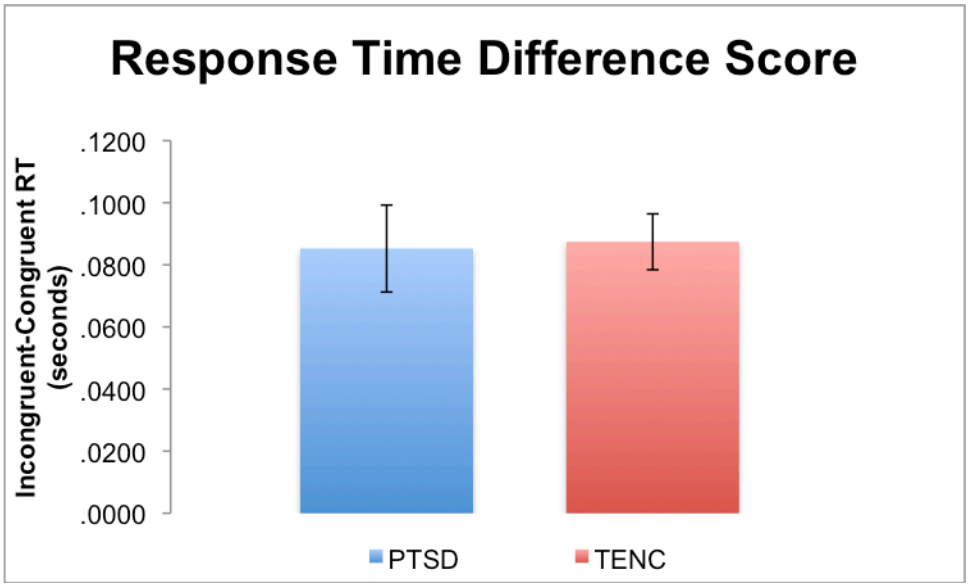



**Figure 4:** Average response time (RT) for the Incongruent vs Congruent trials. Although the Incongruent condition produced a slower RT than the Congruent condition, there was no significant difference between the groups.

We analyzed the response times using a 2(Group: PTSD, TENP) x 2(Condition: Incongruent, Congruent) ANOVA. As expected, there was a main effect of Condition

*F*(1,33)=102.76, *p*<0.001, with faster RTs to the Congruent condition (mean = 0.783 seconds) compared to Incongruent condition (mean = 0.826). However, there was no main effect of group *F*(1,33)=1.696, *p*=0.202. As expected, there was no significant interaction between group and condition *F*(1,33)=0.016, *p*=0.899 (see figure 4).

In tandem with our imaging analyses (see below), we isolated only the Fear and Happy trials and ran two separate ANOVAs for each.

FIvFC RT analysis:

For the analyses with only fear trials (FIvFC), we ran one 2(Group: PTSD, TENP) x 2(Condition: Fear Incongruent, Fear Congruent) ANOVA. As with the IvC ANOVA, there was a main effect of condition *F*(1, 33)=86.866, *p*<0.001, with the faster RTs in the FC condition (mean=0.787) compared to the FI condition (mean=0.833). There was no main effect of group *F*(1,33)=1.853), *p*=0.183 nor an interaction between group and condition *F*(1,33)=0.020, *p*=0.888.

HIvHC RT analysis

For the analyses with only Happy trials (HIvHC), we ran one 2(Group: PTSD, TENP) x 2(Condition: Happy Incongruent, Happy Congruent) ANOVA. As with previous RT analyses, there was a main effect of condition *F*(1,33)=67.376, *p*<0.001, with the faster RTs in the HC condition (mean=0.779) compared to the HI condition (mean=0.819). There was no main effect of group *F*(1,33)=1.431, *p*=0.240 nor an interaction between group and condition *F*(1,33)=0.131, *p*=0.719.

ETKIN BEHAVIORAL REPLICATION:

In an effort to replicate the findings of Etkin and colleagues (2006) we re-analyzed our behavioral data such that each trial reflected the trial that preceded it. We

limited our analysis to the main conditions of interest, High Conflict Resolution and Low Conflict Resolution.

Response time was analyzed using a 2 (Group: PTSD, TENP) x 2 (Condition: HCR, LCR) Mixed Model ANOVA. There was no main effect of Group $F(1,33)=1.554$, $p=0.221$ or Condition $F(1,33)=0.235$, $p=0.235$, nor was there an interaction between the Group and Condition $F(1,33)=2.170$, $p=0.150$.

## FMRI ANALYSES:

### IVC CONTRAST

**Table 1.** Incongruent vs. Congruent for PTSD and TENP within-groups.

| **Activation in PTSD group** | | | **Activation in TENP group** | | |
|---|---|---|---|---|---|
| *Region* | *z Score* | *MNI (x, y, z)* | *Region* | *z Score* | *MNI (x, y, z)* |
| dACC | 3.40 | 12, 4, 42 | rACC | 4.48 | 16, 36, 34 |
| dmPFC | 3.69 | -2, 4, 64 | | 3.27 | -4, 34, 42 |
| | | | | 3.23 | 16, 46, 2 |
| | | | | 3.10 | -10, 42, 32 |
| | | | mPFC | 3.44 | 10, 60, 0 |
| | | | dACC | 3.96 | -12, 4, 44 |
| | | | | 3.33 | -14, 20, 32 |

Within groups analysis:

The PTSD group showed a response in the dACC (12, 4, 42), z=3.40 and the dmPFC (-2, 4, 64), z=3.69. Meanwhile, the TENP group elicited a response in the dACC (-12, 4, 44), z=3.96 as well as the mPFC (10, 60, 0), z=3.44. The TENP group also showed a response in four rACC regions: two lateral regions (16, 36, 34), z=4.48 and (16, 46, 2), z=3.23, as well as two more medial regions (-10, 42, 32), z=3.10 and (-4, 34,

42), z=3.27. For the inverse contrast (CvI), neither group elicited a BOLD response above our threshold of z=3.09.

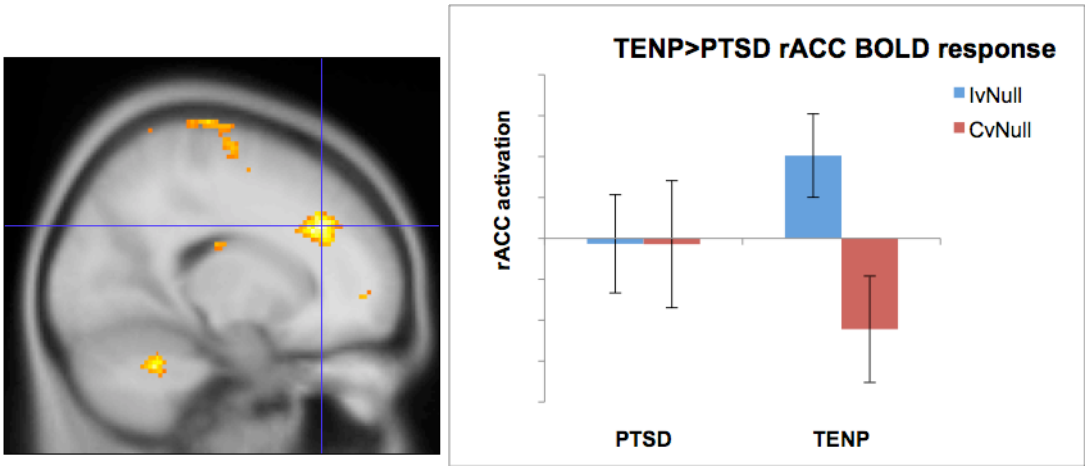



**Figure 5:** In the IvC contrast, the TENP participants produced a significantly greater BOLD response in a lateral rACC region (18, 32, 32), compared to the PTSD group.

| **Table 2.** | Incongruent vs. Congruent<br>Between Group contrasts for PTSD vs. TENP | | | | |
|---|---|---|---|---|---|
| **Greater in PTSD group** | | | **Greater in TENP group** | | |
| *Region* | *z Score* | *MNI (x, y, z)* | *Region* | *z Score* | *MNI (x, y, z)* |
| - | - | - | rACC | 3.57 | 18, 32, 32 |
| | | | dmPFC | 3.09 | 8, 52, 36 |

Between groups analysis:

Between groups, the PTSD group did not significantly activate any regions of interest greater than the TENP group. However, the TENP group exhibited a greater response in the lateral rACC (18, 32, 32), z=3.57 as well as the dmPFC (8, 52, 36), z=3.09, compared to the PTSD group.

IvC Correlations:

Within the PTSD group, we ran a voxelwise whole brain correlation based on the extracted values from the dACC region (12, 4, 42). Based on this analysis, there was a positive correlation between the dACC and the substantia innominata/ dorsal amygdala (-14, -6, -14), z=3.10. See figure 6 for more information.

We ran another voxelwise whole brain correlation, using the current CAPS score of each participant with PTSD. Based on this analysis, there was a negative correlation with the dACC (-8, 24, 28), z=3.74, as well as the mPFC (-18, 48, 14), z=3.66. See figure 7 for more information.

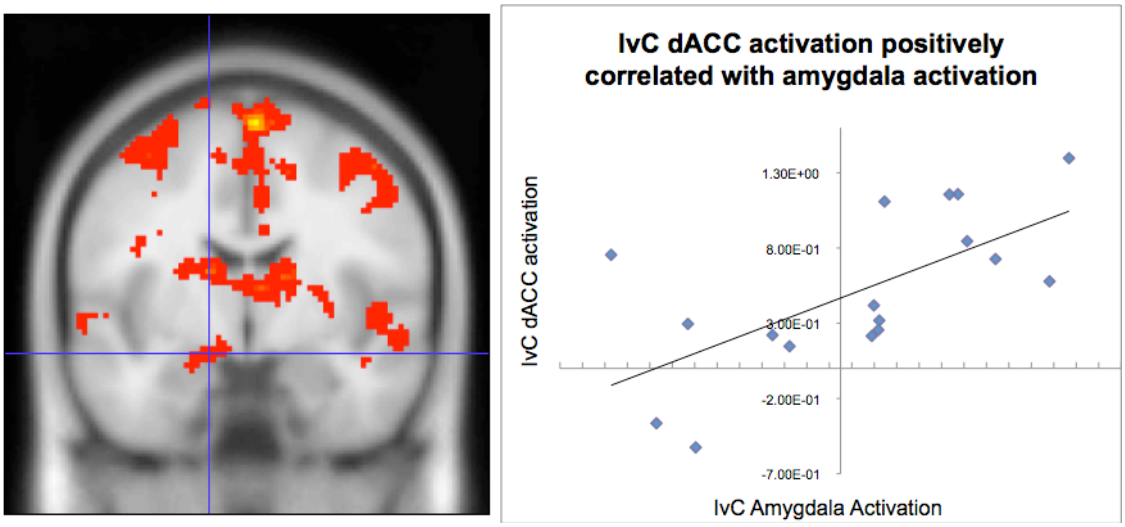
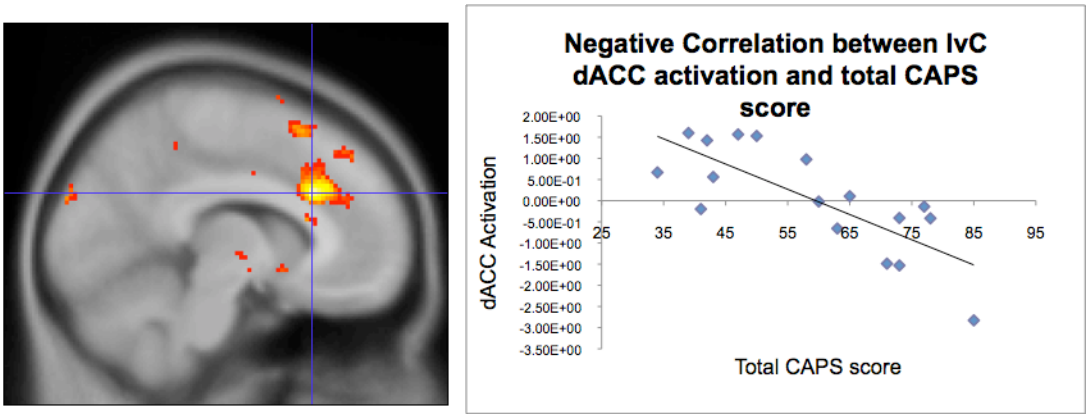



**Figure 6:** For the PTSD group, activation in the dorsal amygdala/ substantia innominata (-14, -6, -14) positively correlated with activation in the dACC.

We tested the hypothesis that the IvC dACC response would negatively correlate with the rACC response. We used a one-sample t-test to define a region where all subjects were producing a BOLD response for the IvC Contrast. Both groups produced a response at the dACC (2, 16, 56) and the rACC at (12, 34, 38) and (14, 44, 2). We extracted values from all three of these regions and ran a correlation between the two rACC regions and the dACC. Unexpectedly, the rACC (12, 34, 38) and dACC (2, 16, 56)

regions *positively* correlated with each other (*r*=0.446, *p*=0.007). The rACC region (14, 44, 2) did not significantly correlate with the dACC (*r*=0.268, *p*=0.120), but it did positively correlate with the other rACC region (12, 34, 38) (*r*=0.432, *p*=0.010).

(A)




(B)

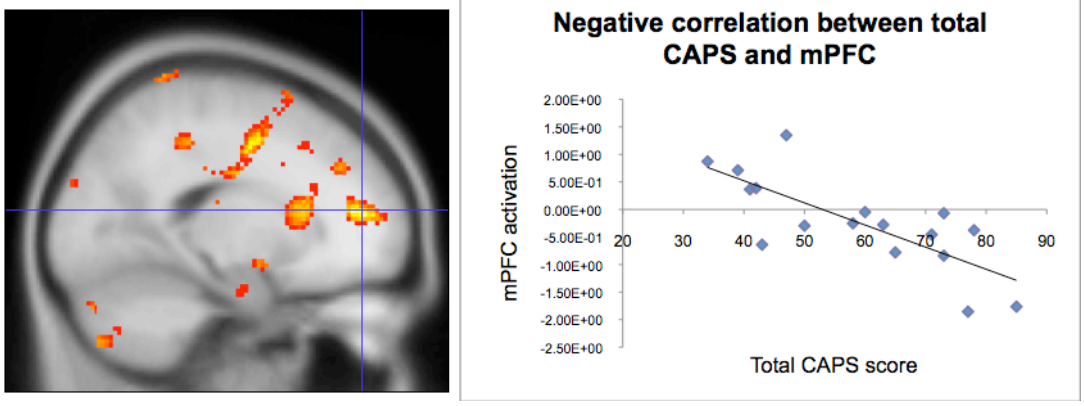



**Figure 7:** In the PTSD group for the lvC contrast, CAPS score negatively correlated with both dACC activation (A) (-8, 24, 28) and mPFC (B) (-18, 48, 14) negatively correlated with CAPS score.

We then examined the possibility that one group was driving these correlations more than the other. For the correlation between the rACC (12, 34, 38) and dACC (2, 16, 56) in the PTSD group, the correlation was reduced to a non-significant trend (*r*=0.440, *p*=0.077), meanwhile for the TENP group, the correlation remained significant (*r*=0.495, *p*=0.037). This may suggest that the positive correlation between the dACC and rACC is stronger in the TENP group.

Regarding the positive correlation between the two rACC regions (12, 34, 38 and 14, 22, 2), there was no significant correlation between the rACC regions in the PTSD group ($r$= 0.341, $p$=0.181). Meanwhile, the correlation between the two rACC regions remained significant within the TENP group ($r$=0.505, $p$=0.033). Given that the effect size for the TENP group ($r$=0.505) was numerically greater than the effect size of both groups together ($r$=0.432), the positive correlation between rACC regions may have been driven by the TENP group.

However, these results looked somewhat different when we used the extracted values from rACC region (14, 44, 2) to produce a voxel-wise whole brain correlation. Within the PTSD group, the rACC positively correlated with the dACC (-12, 16, 32), z=3.96 and the dorsal amygdala (18, -2, -10), z=3.37. Similarly, for the TENP group, the rACC region (14, 44, 2) positively correlated with the dACC (6, 14, 44), z=3.34 and a region anterior to the amygdala (26, 4, -6), z= 3.16. However, for the TENP group, the rACC region also positively correlated with a separate rACC region (-2, 34, 20), z=4.66. These values suggest that in the PTSD group rACC activation exhibited a higher correlation with the dACC and the amygdala, compared to the TENP group. However, the TENP group exhibited a greater correlation with a second rACC region.

We also extracted BOLD activation values from the dACC region (12, 4, 42), defined by the within-subject map and ran a correlation between the extracted values of the PTSD subjects and overall CAPS score. There was no significant correlation between CAPS score and dACC activation values ($p$=0.813).

## IVC CONTRASTS: ISOLATING ONE FACE EMOTION

Given that PTSD is thought to be a disorder of the circuitry involved in fear processing, we examined the IvC contrast in the absence of “happy” trials. The IvC

contrast for fear trials only (or FIvFC) evoked similar responses between groups. We also performed the IvC contrast for happy trials only (HIvHC). The results of the HIvHC and the FIvFC contrasts are discussed below.

FIvFC CONTRAST

| **Table 3.** | Fear Incongruent vs. Fear Congruent for PTSD and TENP within-groups. | | | | |
|---|---|---|---|---|---|
| **Activation in PTSD group** | | | **Activation in TENP group** | | |
| *Region* | *z Score* | *MNI (x, y, z)* | *Region* | *z Score* | *MNI (x, y, z)* |
| MCC | 4.03 | 14, -18, 50 | rACC | 4.86 | 16, 36, 32 |
| | 3.67 | -8, -6, 46 | | 3.80 | 8, 40, 24 |
| dACC | 3.12 | 6, 28, 34 | | 3.68 | -6, 40, 30 |
| | | | dACC | 5.18 | -8, 4, 48 |

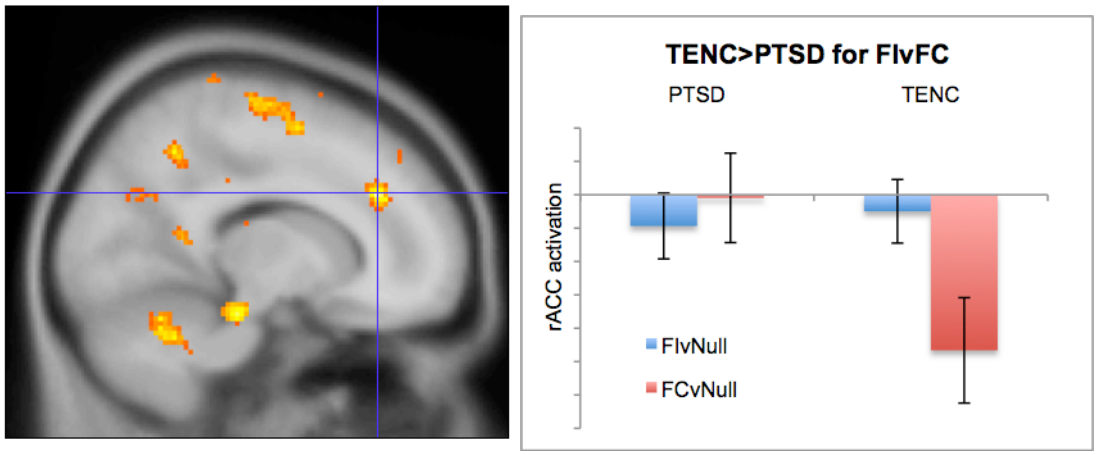
Within Groups analysis:

The PTSD group elicited a BOLD response two regions of the mid-cingulate cortex (MCC) (-8, -6, 46) z=3.67, and (14, -18, 50), z=4.03 as well as the dACC (6, 28, 34), z=3.12. The TENP group elicited a BOLD response in two medial rACC regions (8, 40, 24), z=3.80 (-6, 40, 30), z=3.68 and a more lateral rACC region (16, 36, 32), z=4.86. The TENP group also elicited a BOLD response in the dACC (-8, 4, 48), z=5.18. For the inverse contrast (FCvFI), neither group elicited a BOLD response above our threshold of z=3.09.

Between groups analysis:

The PTSD group elicited a greater BOLD response in the lateral MCC (20, -6, 46), z=3.62 compared to the TENP group. Meanwhile, compared to the PTSD group, the TENP group elicited a greater bold response in two medial rACC regions (6, 36, 18), z=3.25, and (-6, 36, 30), z=3.56, a more lateral rACC (14, 34, 30), z=3.49, the dACC (-6, 4, 50), z=3.13 and the dmPFC (6, 32, 44), z=3.50.

(A)




(B)

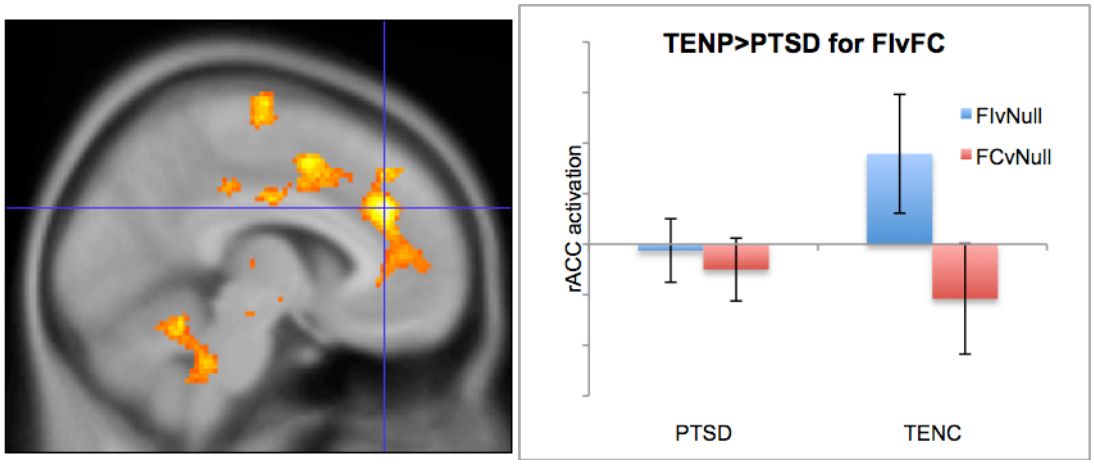


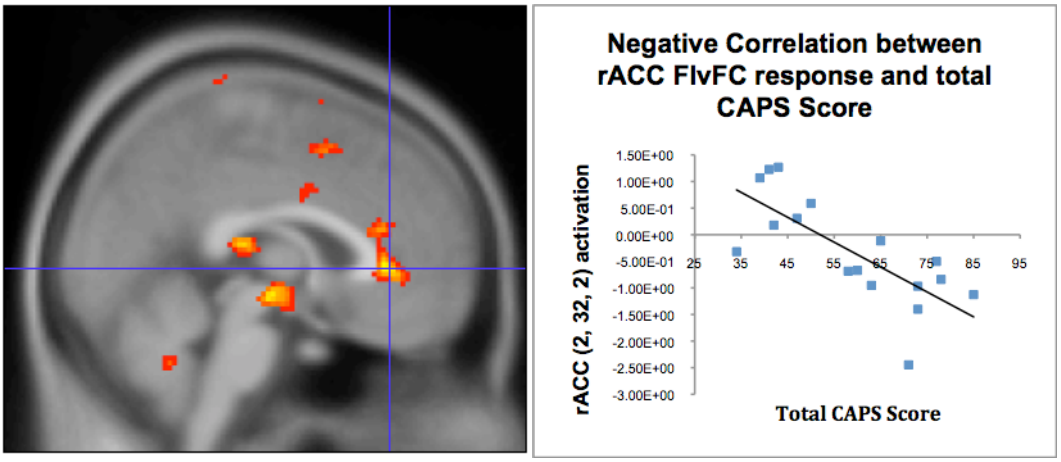

**Figure 8:** In the FIvFC contrast, the TENP participants produced a significantly greater BOLD response in the rACC (A) (-6, 36, 30) and the lateral rACC region (B) (14, 34, 30), compared to the PTSD group.

| **Table 4.** | Fear Incongruent vs. Fear Congruent Between Group contrasts for PTSD vs. TENP | | | | |
|---|---|---|---|---|---|
| **Greater in PTSD group** | | | **Greater in TENP group** | | |
| *Region* | *z Score* | *MNI (x, y, z)* | *Region* | *z Score* | *MNI (x, y, z)* |
| Lateral MCC | 3.62 | 20, -6, 46 | rACC | 3.56 | -6, 36, 30 |
| | | | | 3.49 | 14, 34, 30 |
| | | | | 3.25 | 6, 36, 18 |
| | | | dACC | 3.13 | -6, 4, 50 |
| | | | dmPFC | 3.50 | 6, 32, 44 |

FIvFC Correlations:

For the PTSD group only, we ran a voxel wise whole brain correlation with total CAPS score. We report a negative correlation between total CAPS score and the two separate rACC regions (2, 34, 2) z=3.47 and (12, 40, 8), z=3.74).

A)




B)

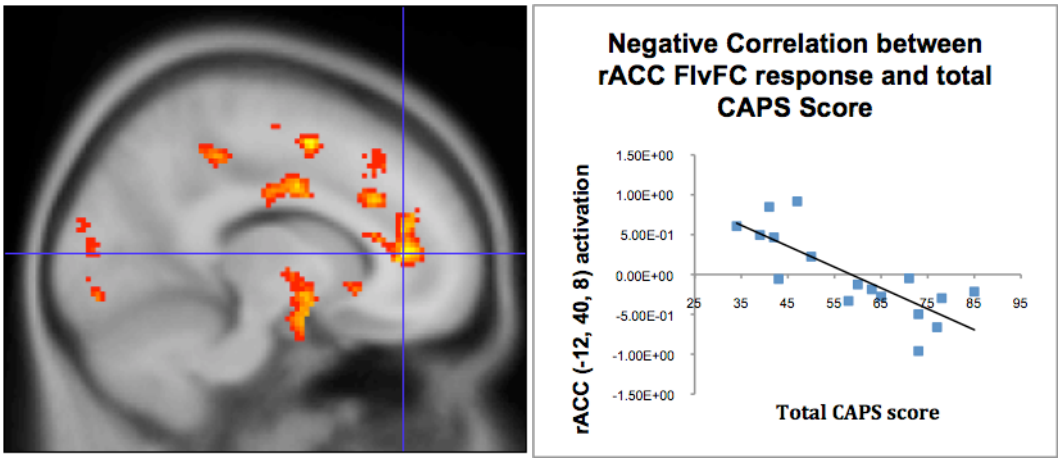



**Figure 9**: Voxel-wise whole brain correlation with total CAPS score. A significant, negative correlation is reported for two rACC regions. A) (2, 32, 2), z=3.47 B) (12, 40, 8), z=3.74.

### HIvHC CONTRAST

Within groups analysis:

The PTSD group did not elicit any significant BOLD responses in our a priori regions of interest. BOLD responses outside of our ROIs did not reach our a posteriori threshold. The TENP group elicited a significant BOLD response in the lateral rACC (18, 34, 26), z=3.09. For the inverse contrast (HCvHI), neither group elicited a BOLD response above our threshold of z=3.09.

| **Table 5.** | Happy Incongruent vs. Happy Congruent for PTSD and TENP within-groups. | | | | |
|---|---|---|---|---|---|
| **Activation in PTSD group** | | | **Activation in TENP group** | | |
| *Region* | *z Score* | *MNI (x, y, z)* | *Region* | *z Score* | *MNI (x, y, z)* |
| - | - | - | Lateral rACC | 3.09 | 18, 34, 26 |

Between groups analysis:

The PTSD group did not produce any significant BOLD responses, in comparison to the TENP group. However, compared to the PTSD group, the TENP group elicited a significant BOLD response in the lateral portion of the dACC (20, 26, 30), z=3.37.

| **Table 6.** | Fear Incongruent vs. Fear Congruent Between Group contrasts for PTSD vs. TENP | | | | |
|---|---|---|---|---|---|
| **Greater in PTSD group** | | | **Greater in TENP group** | | |
| *Region* | *z Score* | *MNI (x, y, z)* | *Region* | *z Score* | *MNI (x, y, z)* |
| - | - | - | Lateral dACC | 3.37 | 20, 26, 30 |

### FVH CONTRAST

Previous evidence has indicated that participants with PTSD elicit differential amygdala and medial prefrontal cortex responses to Fear faces, compared to Happy faces (Shin et al., 2005). In order to explore this with our current data set, we contrasted

the Fear condition against the Happy condition (FvH contrast). The results of the FvH contrast are discussed below.

| **Table 7.** | Fear vs. Happy for PTSD and TENP within-groups. | | | | |
|---|---|---|---|---|---|
| **Activation in PTSD group** | | | **Activation in TENP group** | | |
| *Region* | *z Score* | *MNI (x, y, z)* | *Region* | *z Score* | *MNI (x, y, z)* |
| - | - | - | SI/amygala | 3.10 | 20, -8, -10 |

| **Table 8.** | Fear vs. Happy for PTSD and TENP within-groups. | | | | |
|---|---|---|---|---|---|
| **Deactivation in PTSD group** | | | **Deactivation in TENP group** | | |
| *Region* | *z Score* | *MNI (x, y, z)* | *Region* | *z Score* | *MNI (x, y, z)* |
| rACC | 3.29 | 2, 42, 16 | rACC | 3.35 | -2, 52, 16 |
| dmPFC | 3.33 | 6, 54, 26 | | 3.23 | -6, 36, 12 |
| | | | mPFC | 3.83 | 2, 56, 2 |
| | | | dACC | 4.02 | -6, 28, 44 |

Within groups analysis:

The PTSD group did not produce any significant BOLD responses to Fear faces, compared to the Happy faces. However, this group did elicit a BOLD deactivation in the rACC (2, 42, 16), z=3.29 as well as a region in the dmPFC (6, 54, 26), z=3.33.

The TENP group elicited a significant BOLD response in the substantia innominata (SI) (20, -8, -10), z=3.10. Meanwhile this group produced a BOLD deactivation in two rACC regions (-2, 52, 16), z=3.35 and (-6, 36, 12), z=3.23, the mPFC (2, 56, 2), z=3.83 as well as the dACC (-6, 28, 44), z=4.02.

Between groups analysis:

The two groups did not significantly differ in terms of BOLD signal increases or decreases to Fear vs. Happy face trials.

### HCRvLCR CONTRAST (ETKIN REPLICATION):

We also analyzed our data in a way to replicate a previous Face Stroop publication (Etkin et al., 2006). To this end, we examined High Conflict Resolution (HCR) trials, compared to Low Conflict Resolution (LCR) trials.

Within Group Analysis :

The PTSD group elicited a significant increase in BOLD activation in two medial dACC regions (0, 26, 14), z=4.70, (8, 26, 28), z=3.52 and a more lateral dACC region (-16, 10, 46), z=3.65. This group also elicited an increase in BOLD activation in two dmPFC regions (-14, 52, 20), z=3.49 and (4, 54, 24), z=3.12 as well as the mPFC (-12, 52, -4), z=3.17. The PTSD group also elicited an increase in the amygdala hippocampal area (AHA) (-22, -14, -28), z=4.03.

**Table 9.** HCR vs. LCR for PTSD and TENP within-groups.

| **Activation in PTSD group** | | | **Activation in TENP group** | | |
|---|---|---|---|---|---|
| *Region* | *z Score* | *MNI (x, y, z)* | *Region* | *z Score* | *MNI (x, y, z)* |
| dACC | 4.70 | 0, 26, 14 | rACC | 3.55 | 12, 34, 26 |
| | 3.65 | -16, 10, 46 | dACC | 3.18 | 14, 10, 34 |
| | 3.52 | 8, 26, 28 | | 3.13 | 14, 14, 36 |
| dmPFC | 3.49 | -14, 52, 20 | dmPFC | 3.80 | -2, 36, 30 |
| | 3.12 | 4, 54, 24 | | 3.48 | 10, 54, 34 |
| mPFC | 3.17 | -12, 52, -4 | | | |
| Hipp/AHA | 4.03 | -22, -14, -28 | | | |

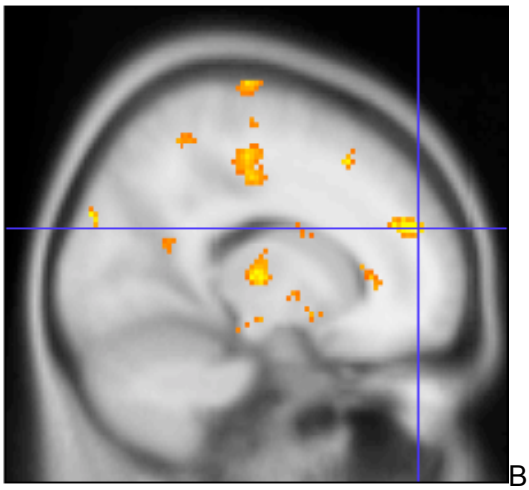
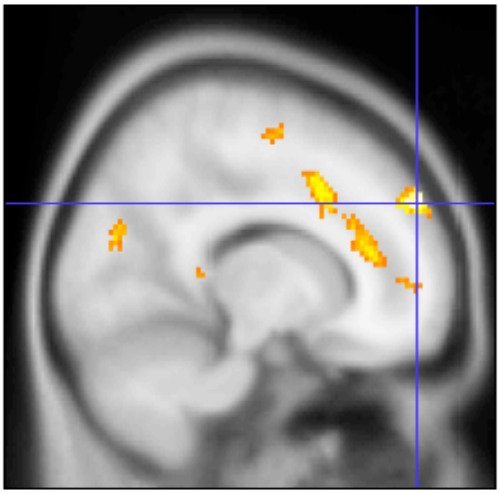
A)  B) 

**Figure 10:** In the HCRvLCR contrast, the PTSD group produced a significantly greater BOLD response in the dmPFC compared to the TENP group (A). For the same contrast, the TENP group also produced a significantly greater BOLD response in the dmPFC compared to the PTSD group (B). The two regions are about a centimeter apart.

The TENP group elicited a significant increase in BOLD activation in the rACC (12, 34, 26), z=3.55 as well as two regions of the dACC (14, 14, 36), z=3.13 and (14, 10, 34), z=3.18. This group also elicited an increase in BOLD activation in two dmPFC regions (-2, 36, 30), z=3.80 and (10, 54, 34), z=3.48.

| **Table 10.** | HCR vs. LCR<br>Between group contrast for PTSD vs TENP | | | | |
|---|---|---|---|---|---|
| **Greater in PTSD group** | | | **Greater in TENP group** | | |
| *Region* | *z Score* | *MNI (x, y, z)* | *Region* | *z Score* | *MNI (x, y, z)* |
| dmPFC | 3.15 | 16, 52, 24 | dmPFC | 3.54 | 14, 56, 34 |

Between Group analysis:

The PTSD group elicited a greater increase in BOLD activation in the dmPFC (16, 52, 24), z=3.15 as compared to the TENP group (see figure 10A).

The TENP group also elicited a greater increase in BOLD activation in the dmPFC (14, 56, 34) z=3.54 compared to the PTSD group (see figure 10B).

## DISCUSSION

### BEHAVIORAL FINDINGS:

It was hypothesized that the subjects would have lower error rates and faster response times in the congruent, compared to the incongruent condition. These hypotheses were supported by our data, indicating that the incongruent condition was more difficult than the congruent condition.

It was also hypothesized that the PTSD group would have significantly higher error rates and slower response times overall compared to the TENP group. This was not supported by our data; there seemed to be no difference between groups. This may have been because the Face Stroop relied on trauma-unrelated emotional stimuli. Previous emotional Stroop tasks have almost exclusively reported a between group difference in overall response time for trauma-related (McNally et al., 1990; Cassiday et al., 1992) emotional stimuli.

We did not hypothesize that participants with PTSD would be significantly slower than TENPs in response time during the incongruent, compared to the congruent condition. Indeed, no significant condition by group interaction was reported.

### Behavioral Findings for Etkin replication:

We were unable to replicate the behavioral findings of Etkin and Colleagues (2006), which reported significantly higher response times for Low Conflict Resolution (LCR) compared to High Conflict Resolution (HCR). In addition, the PTSD group did not differ from the TENP group overall, or as an interaction between group and condition.

### RACC FINDINGS:

It was predicted that the TENP group would exhibit greater rACC BOLD responsivity in the Incongruent vs Congruent (IvC) contrast than the PTSD group. Our

data partially supported this hypothesis, with the TENP group eliciting a greater BOLD response in a lateral (x=18) region of the rACC. This region may be too lateral to be considered a part of the rACC gray matter. However, considering the extent of the Gaussian smoothing kernel (7mm), it is possible that the actual center of this response is a few millimeters away, and within the boundaries of the cingulate gray matter. Furthermore, this region was not limited to the reported peak activation it extends medially into the classically defined cingulate gyrus.

Overall, these results support our hypothesis that patients with PTSD would exhibit rACC hyporesponsivity, relative to the TENP participants during emotional interference involving trauma-unrelated emotional stimuli. This supports the hypothesis that patients with PTSD process emotional stimuli differently than TENP participants during emotional interference.

rACC Correlations

It was predicted that the IvC BOLD activation in the rACC, for the PTSD group, would negatively correlate with current scores on the Clinician Administered PTSD Scale (CAPS). This inverse correlation would provide evidence for a relationship between the emotional interference and symptom severity of PTSD. Our results provide support for this hypothesis. Using a voxel-wise whole-brain correlation, the rACC did not negatively correlate with CAPS score. However, the mPFC, a larger region that encompasses the rACC was found to negatively correlate with current CAPS score.

Once we limited our IvC analysis to only Fear trials, much of the variance produced from different emotional expressions was reduced. We then ran another voxel-wise whole brain correlation for total CAPS score in the PTSD group. This revealed two distinct regions of the rACC that negatively correlated with total CAPS score, supporting our hypothesis that the rACC BOLD response would negatively correlate with PTSD

symptoms. This also supports previous research, which suggests that rACC BOLD response is inversely related to PTSD symptoms (Shin et al., 2005, Hopper et al., 2007).

For the PTSD group, we also found a negative correlation between the dACC and total CAPS score. This was unexpected, considering previous publications where dACC activity positively correlated with CAPS score (Shin et al., 2009). However, Shin and colleagues reported their region to be closer to the mid-cingulate cortex (y=2), whereas the dACC that we reported to negatively correlate with CAPS score was closer to the rACC (y=24). The y-value cutoff between the rACC and dACC is y=30 (Bush et al., 2002) and while this cutoff has proven to be reliable, there is some overlap between what is considered to be the rostral and dorsal cingulate (Bush et al., 2000). In other words, some cognitive tasks elicit an activation at y>30 and some emotional tasks elicit and activation at y<30 (Bush et al., 2000, Shin et al., 2001).

### DACC FINDINGS:

The PTSD group was predicted to display greater IvC BOLD responsivity in the dACC, relative to the TENP group. This was not supported by our data. Both groups elicited an increase in BOLD response in the dACC, but neither of them significantly differed from the other.

We hypothesized that the dACC activation in the IvC contrast would positively correlate with current CAPS scores in the PTSD group. Using a voxel-wise, whole brain correlation, our data did not support this hypothesis (see above). If we were to consider the observed activation (-8, 24, 28) as the dACC, the correlation between dACC and CAPS score would not be above our *a posteriori* threshold. We also extracted activation values from the dACC in the PTSD group and these values also did not correlate with total CAPS score. Overall, we did not find support for our hypothesis that dACC activation would positively correlate with total CAPS score.

It was also hypothesized for both groups that the dACC activation in the IvC contrast would positively correlate with the difference in response times between Incongruent and Congruent trials. This was not supported by our results. For both groups in the IvC contrast, BOLD responses in the dACC were predicted to inversely correlate with the BOLD responses in the rACC. We reported a positive correlation between the rACC and dACC extracted values, so this hypothesis was not supported.

It is possible that the previous reports of dACC hyperresponsivity are entirely task dependent. Many times they involve either the expression of a fear or arousal response (Bremner et al., 2005; Felmingham et al., 2009; Milad et al., 2009) or a task involving neutral stimuli (Shin et al., 2007; Bryant et al., 2005). In the instances where emotional interference is involved, the dACC appears in both groups (Shin et al., 2001), which is similar to our results. The most convincing connection between the dACC and PTSD is a measurement of resting glucose metabolism in patients with PTSD and their non-symptomatic identical co-twin (Shin et al., 2009). Although this study reported a positive correlation between CAPS score and dACC activity, resting glucose metabolism may not be comparable to fMRI BOLD responses during an emotional interference task.

### AMYGDALA FINDINGS:

Amygdala activation in the IvC contrast was hypothesized to positively correlate with current CAPS scores. Our data from the voxel-wise whole brain correlation with CAPS score did not support this hypothesis. For the same contrast, it was predicted that BOLD responses in the amygdala would positively correlate with BOLD responses in the dACC, but negatively correlate with the rACC. The results from our voxel wise correlation supported the prediction that the dACC would positively correlate with amygdala activation. However, our data did not support the hypothesis that amygdala activation was negatively correlated with rACC activation. Neither the PTSD nor the

TENP group showed a significant increase in amygdala BOLD response for the IvC contrast and there was no difference between the two groups. This meant that we could not run a correlation between extracted values of the amygdala and rACC, nor could we run a whole brain correlation with extracted values from the amygdala.

Furthermore, we reported a positive correlation in the PTSD group between the rACC region (14, 44, 2), and the dorsal amygdala. Comparatively, the TENP group did not exhibit a positive or negative correlation with the amygdala, although we did find a positive correlation with a region just anterior to the amygdala. Overall, we did not find any evidence for a negative correlation between the rACC and amygdala.

We also predicted that the amygdala would increase in responsivity for the FvH contrast. This was partially supported, in that the TENP group (but not the PTSD group) elicited an increased substantia innominata (SI) BOLD response for the FvH contrast. The SI is a region that is connected to the amygdala, and although it is not classically considered to be a part of the amygdala, it is considered to be a part of the *extended amygdala* (Davis and Whalen, 2001). In addition, we predicted that the FvH BOLD response would be greater for participants with PTSD, but this was not the case.

The lack of a true amygdala response was surprising, since the FvH contrast should have been analogous to contrasts used in studies in which fearful versus happy faces were compared (Morris et al., 1996). However, SI response has been previously documented in fear faces compared to angry faces (Kim et al., 2003b). It was also surprising that the PTSD group did not elicit an amygdala response for the FvH contrast, since similar studies have reported a greater amygdala response in the PTSD group for fearful vs. happy facial expressions (Shin et al., 2005; Williams et al., 2006).

The main difference between our FvH contrast and previous studies that used emotional faces is that our Fear and Happy faces were labeled with either the correct or incorrect emotion. Furthermore, the subjects were not passively viewing the faces, as

they would be in previous emotional face tasks. Some research has indicated that labeling an emotional face with an emotional label (such as fearful or happy) reduces rCBF to the amygdala (Hariri et al., 2000). Perhaps either the labels on the faces, the emotion labeling task or a combination of the two significantly reduced amygdala responsivity. Overall, these findings did not support our hypothesis, which predicted greater amygdala BOLD activation in the PTSD, rather than the TENP group.

### fMRI FINDINGS OF THE ETKIN REPLICATION:

Etkin et al., (2006) reported an increase in rACC responsivity during the HCR condition, compared to the LCR condition (HCRvLCR contrast). We report similar results in our sample, with an rACC response in the TENP group, but not the PTSD group.

However, Etkin et al., (2006) also reported an increase in dmPFC responsivity during the LCR condition, compared to the HCR condition. We did not replicate these results in our sample, but we do report an increase in dmPFC responsivity in the opposite direction - during the HCR condition, compared to the LCR condition.

More interestingly, both the PTSD and the TENP group elicited a relative increase in the dmPFC, relative to one another, for the HCRvLCR contrast. This may indicate that the two groups recruited slightly different regions of the dmPFC during the HCR condition, compared to the LCR condition.

## Limitations and Future Directions

One important caveat is that we hypothesized a functional distinction between dACC and rACC. This was based on previous work, which has suggested that the rACC is involved in emotional interference and the dACC is involved in cognitive interference (Bush et al., 2000; 2002). Bush and colleagues estimated that the division between the rostral and dorsal cingulate areas is about y=30. However, the interference from the

Face Stroop produced a peak region of activation at y=32 and likely recruited part of the dACC as well as the rACC. So although our peak activation was within the boundaries that we predicted, it would not be accurate to say that *only* the rACC was recruited to mitigate the emotional interference involved in the Face Stroop. Furthermore, it would not be accurate to say that patients with PTSD exhibited hyporesponsivity of *only* the rACC.

A recent review article by Etkin and colleagues may frame the results in a new light (Etkin et al., 2011). Here the authors suggest that the dACC should not be characterized as a purely "cognitive" region, as suggested by Bush et al., 2000. Rather, they suggest that the dACC is involved in the appraisal and expression of negative emotion. Certainly the Face Stroop not only involves the appraisal of emotion, it more specifically relies on the conflict in the appraisal of emotion. Given this new theoretical framework, it is not surprising to observe a region with a peak activation of y=32. Additionally, this may explain our inverse relationship between dACC BOLD response and PTSD symptom severity.

Within the theoretical framework from Etkin and colleagues, our results suggest that patients with PTSD may be exhibiting brain response differences during emotional appraisal. This framework allows us to examine the inverse correlation between dACC and CAPS score in a new light. Here, the recruitment of the cingulate during emotional appraisal is inversely correlated with symptom severity. This dovetails with previous findings, which suggest that patients with PTSD have difficulty identifying their own emotions (or alexithymia) (Frewen et al., 2006; 2008). Although it is unclear if identifying one's own emotions and identifying photos of facial emotions is directly comparable, it is possible that the two processes share some of the same cognitive machinery. Indeed, Frewen and colleagues have reported a negative correlation between alexithymia and rACC (y=32) BOLD response during script driven imagery (Frewen et al., 2008). Future

research could explore the relationship between cingulate function, alexithymia and the identification of face emotions.

It is also possible that we encountered a ceiling effect with the Face Stroop. Although the Incongruent condition proved to be more difficult than the Congruent, the average RT difference was only 43 ms. In addition the average difference in error rates was 1.74%, however this number does increase to 3.9% if non-responses are included in the analysis.

This indicates that we may have encountered a ceiling effect with regard to the difficulty of our task, which may have resulted in relatively reduced effect sizes. Additional problems with this data set may have arisen from recruiting some PTSD subjects with less severe symptoms. This may have added some noise to our sample and decreased the likelihood of finding any between subject effects. This may have been due to our choice to exclude patients on medication, since the more severe patients with PTSD may be more likely to seek out pharmacotherapy. In support of this, our average CAPS score for the PTSD group was 58.76; while the CAPS score average for our lab's previous publications (Shin et al., 1997; 1999; 2001; 2004; 2005; 2007; 2009) is 69.2.

Additionally, four of our patients were diagnosed with co-morbid major depression. We therefore explored the possibility that co-morbid major depression accounted for a confounding factor. When we removed these four subjects from the analysis, the results looked nearly identical except for a reduced effect size from the loss of power.

Another potential problem with these data is that all of our subjects completed an emotional memory paradigm before beginning the Face Stroop. During the Face Stroop, many of the subjects became fatigued, sometimes missing several of the trials or entire runs. Eliminating subjects with high errors reduced our *n* and eliminating missed trials decreased our power. Furthermore, previous research has suggested that fatigued

subjects exhibit changes in cingulate blood flow (Lim et al., 2010). Although we could eliminate incorrect or omitted trials from the Face Stroop, we had no way of eliminating fatigued subjects who continued to respond correctly. Therefore we could not account for altered brain responses due to cognitive fatigue.

Future research should focus on eliminating unnecessary noise from patients with lower CAPS scores and fatigued subjects. Furthermore, controlling for the effect of happy trials enhanced many of our results and any replication of the Face Stroop may examine the effect of IvC contrast in Fear trials exclusively.

## CONCLUSION

We tested the hypothesis the patients with PTSD would exhibit an attenuated rACC BOLD response during an emotional interference task, which utilized trauma-unrelated stimuli. This hypothesis was supported by our findings and overall the Face Stroop elicited a significantly greater rACC BOLD response in the TENP group, compared to the PTSD group. We also hypothesized a positive correlation between the dACC and dorsal amygdala/SI. Our results support previous our hypothesis as well as evidence which suggests a functional (Roy et al., 2009) and anatomical (Morecraft et al., 2007) connection between the dACC and dorsal amygdala. Additionally, we tested the hypothesis that the PTSD group would have greater dACC activation than the TENP group, but this was not supported by our results.

Overall, our results provide evidence that patients with PTSD are differentially appraising trauma-unrelated emotional stimuli during emotional interference. These findings support previous theoretical work indicating that patients with PTSD exhibit difficulty with emotional interference (McNally, 1998).

Furthermore, the rACC BOLD response in the FI vs FC comparison was inversely proportional to PTSD group's symptom severity. This supports previous work,

suggesting that the pathology of PTSD may be due to functional abnormalities in the brain's fear neurocircuitry (Shin and Handwerger et al., 2009).

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