The Origin of Concentration Problems in Posttraumatic Stress Disorder

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Abstract

Posttraumatic stress disorder (PTSD) is an often-debilitating psychiatric disorder that emerges in some individuals after experiencing a traumatic event. Hyperarousal-related symptoms include "problems with concentration" and most related research demonstrates that trauma-related and emotional cues are particularly distracting for individuals with PTSD. Neurocircuitry models of PTSD have revealed functional abnormalities in fear memory-related structures such as the dorsal anterior cingulate cortex (dACC), further emphasizing the traumatic event and emotion. However, the dACC is involved in processes other than fear memory expression, such as exertion and maintenance of top-down cognitive control that prevents potentially distracting cues from capturing attention. The current studies aim to determine whether PTSD is associated with such fundamental impairment to the top-down attention system that even trauma-unrelated, emotionally neutral stimuli can disrupt concentration by capturing attention. They also address the origin of concentration problems and functional brain abnormalities, which may be acquired characteristics of PTSD or of trauma exposure, or may reflect pre-existing familial vulnerability to PTSD. We used two non-emotional paradigms, the Posner Cueing Task and the Multi-Source Interference Task (MSIT), to assess the propensity for attentional capture and dACC function in PTSD. The Posner task was presented to two participant groups: 1) Vietnam War combat veterans with or without current PTSD and their combat-unexposed monozygotic twins, and 2) undergraduates with varying levels

of trauma exposure. Veterans with PTSD and their cotwins were more prone to exogenous attentional capture than veterans without PTSD and their cotwins, demonstrating that this abnormality is a familial vulnerability factor. As further evidence of this vulnerability factor, exogenous attentional capture in combat-unexposed individuals correlated with PTSD hyperarousal symptoms in their combat-exposed identical twins. The undergraduate cohort produced null findings. The MSIT task, which reliably activates the dACC of healthy individuals, was presented to the twin cohort during fMRI. The results demonstrated that dACC hyperresponsiveness during the MSIT task is a familial vulnerability factor. These results are discussed in the context of dACC functions such as cognitive control and the detection of stressor controllability.

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I. INTRODUCTION

A. PTSD REVIEW

Posttraumatic stress disorder (PTSD) is an often-debilitating psychiatric disorder that emerges in some people after experiencing a traumatic event. The recent DSM-5 (APA, 2013) has shifted the categorization of PTSD from "anxiety disorder" to a "trauma- and stress-or-related disorder," emphasizing its relationship to the triggering trauma. Indeed, the most influential model of PTSD is the fear conditioning model, which treats the triggering trauma as a Pavlovian unconditioned stimulus and therefore considers many symptoms to be conditioned responses (Orr et al., 2000; Pitman & Orr, 1986; VanElzakker, Dahlgren, Davis, Dubois, & Shin, 2014). Symptoms tend to be directly related to the trauma (i.e. recurrent nightmares about it), or are generally assumed by the field to be trauma-related. For example, according to criterion E5, individuals with PTSD predictably have "problems with concentration." Such problems with concentration and attention in PTSD are considered to be reflective of "Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred" (APA, 2013).

Given this implied direct relationship with the traumatic event, most attention and executive function research related to “problems with concentration” has utilized trauma-related stimuli. For example, words like “FIRE” increase Stroop task interference in burn victims with PTSD (Sveen, Dyster-Aas,

& Willebrand, 2009). Indeed, it is well established that individuals with PTSD show attentional bias towards trauma-related and emotional stimuli (reviewed in (Hayes, VanElzakker, & Shin, 2012). A broader question to ask is whether PTSD is associated with such fundamental disruption to the attention system that even trauma-unrelated, emotionally neutral stimuli can be used to distract attention and disrupt concentration.

Do problems with attention in PTSD exist at a much more fundamental level than the DSM assumes? And if problems with attention in PTSD involve fundamental attentional neurocircuitry, from where do those problems arise - after the experience of trauma regardless of PTSD diagnosis, only after PTSD takes hold, or are they actually a vulnerability for PTSD? At the neural level, how could problems with concentration relate to a traumatic experience? In this dissertation, I will provide background into the attention literature, first describing the characterization of dual attentional systems and then describing the Attention to Memory (AtM) hypothesis. The Attention to Memory hypothesis ties the mechanisms and anatomy of top-down and bottom-up attention to the phenomenon of episodic memory. These concepts, elucidated in healthy individuals, will then be related to a novel hypothesis of concentration problems in PTSD. This hypothesis advances the idea that, to the detriment of the top-down neural circuitry that allows for deliberate attention and focused concentration, individuals with PTSD have defaulted to the bottom-up attentional system that is captured by salient stimuli in the environment, even when those

stimuli are unrelated to trauma and are emotionally neutral. I will describe a series of experiments designed not only to better explicate the nature of attentional dysfunction in PTSD, but also to uncover whether such dysfunction is an emergent symptom of PTSD, a consequence of trauma exposure, or a familial vulnerability factor for developing PTSD after trauma exposure. We use the term "familial" because our design does not enable us to determine whether such a vulnerability would reflect shared genes, shared environment, or some combination. In the current studies, attention will be assessed using two paradigms: a Posner Cueing Task and the Multi-Source Interference Task (MSIT). The results will be described in terms of their role as familial vulnerability factors for PTSD. The discussion will consider the matter by which both genes and environment could lead to such a vulnerability factor, and the manner by which such a vulnerability factor could serve to give rise to PTSD. In doing so, I will integrate the animal stressor controllability literature into the human PTSD literature. The distinction between top-down and bottom-up in the attention system is discussed in the next section.

B. BASIC ATTENTION REVIEW

The process of attention has been divided into top-down (endogenous or voluntary) and bottom-up (exogenous or involuntary), a distinction now referred to as dual attentional systems (Corbetta & Shulman, 2002). In practical terms, this distinction represents the difference between purposefully seeking or paying

attention to some stimulus, and having some external stimulus capture one's attention. For example, if Heather is looking through a crowd for a friend wearing a red t-shirt, Heather is engaged in endogenous, goal-driven attention. This is a voluntary process in which attention is deliberately recruited to accomplish some goal vis-a-vis the external environment: in this case, searching for a friend. However, if a red balloon suddenly floats up from the crowd, Heather is likely to notice it even though she was looking for something else. In fact, she will probably detect the balloon, disengage from the deliberate search for her friend, shift her attention to the balloon, and then pay attention to it (rather than to the search for her friend), if only for a moment (Posner, 1980). This is exogenous attentional capture - a stimulus-driven and involuntary response to a salient or novel stimulus in the environment. It is considered bottom-up because an environmental cue engages the cognitive process of attention as opposed to top-down attention that deliberately engages the environment. The ability to resist exogenous attentional capture is one of many functions broadly referred to as cognitive control, and a key brain structure subserving cognitive control, the anterior cingulate cortex, will be the main focus of this dissertation. But first, brain circuits underlying endogenous (top-down) and exogenous (bottom-up) attention will be described.

The neural circuitry of the dual attentional systems has been fairly well described. Broadly, the distinction between endogenous and exogenous attentional systems is represented by dorsal (superior) and ventral (inferior)

frontoparietal circuits, respectively (Corbetta & Shulman, 2002; Vossel, Weidner, Driver, Friston, & Fink, 2012). These are called the dorsal and ventral attention networks. (Helpfully, "dorsal" means "*top* of the brain" and serves *top*-down or endogenous processes while "ventral" means "*bottom* of the brain" and serves *bottom*-up or exogenous processes.) More specifically, the dorsal attention network (DAN) consists of frontal eye fields (FEF), middle temporal complex, and the intraparietal sulcus/superior parietal lobe (IPS/SPL). The ventral attention network (VAN) is generally right-lateralized and includes ventral frontal cortex, insular cortex, and the temporoparietal junction. Along with the VAN, exogenously-driven attention also frequently activates the precuneus (Shulman & Corbetta, 2004). As a neural circuit that is engaged during deliberate attentional tasks, the resting-state DAN is anticorrelated with the resting-state default network (reviewed in Shulman & Corbetta, 2004). This may represent switching mental state in and out of deliberate attention during resting-state scans. The key structure in the anticipation of tasks demanding increased attention or cognitive control, thus triggering such switches, is the dorsal anterior cingulate cortex or dACC (Shackman et al., 2011; Shenhav, Botvinick, & Cohen, 2013; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). While this dual attentional systems account elegantly delineates the relationship between cognitive attention and the external environment, its principles have been extended to the "environment" of episodic memories. The AtM hypothesis of Moscovitch, Ciaramelli, Olson, Grady and Cabeza (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Ciaramelli, Grady,

& Moscovitch, 2008) is based on the observation of parietal cortex activation during episodic memory retrieval tasks.

C. ATTENTION TO MEMORY (AtM)

Before the advent of functional neuroimaging, neurologists would not have suspected that the parietal cortex was particularly involved in memory (reviewed in (Cabeza et al., 2008). This is because parietal cortex lesions do not tend to give rise to the types of catastrophic episodic memory deficits seen with medial temporal lobe lesions. Parietal cortex lesions are instead associated with attentional dysfunction, such as spatial neglect. However, it became clear that the parietal lobe is somehow involved in episodic memory retrieval as soon as the first ERP and PET scans allowed for functional imaging of the brain during ongoing cognitive tasks. Intriguingly, episodic memory retrieval tasks caused functional activity in the same areas of posterior parietal cortex involved in attentional tasks.

Moscovitch, Cabeza, and colleagues hypothesize that the important contribution of parietal cortex to episodic memory retrieval may be, just like in the attention literature, endogenous vs. exogenous (Ciaramelli et al., 2008). The key concept in understanding how episodic memory recall can be considered an exogenous process is the notion that a memory can itself be an attention-demanding stimulus. The famous example of this is from the protagonist of Marcel Proust's novel In Search Of Lost Time (also translated as Remembrance

of Things Past; Proust 1913). When the taste of a madeleine cake dunked in tea triggers a massive flood of autobiographical episodic memories, the outpouring of memories dominate attentional resources, consuming consciousness. The memories themselves have become like a shooting star capturing and dominating the attention of a stargazer. In the Proustian example, the memory recalled is involuntary (similar to a PTSD flashback, see below) but any interesting or salient or unexpected memory can capture attentional resources. Continuing with the analogy, the AtM hypothesis regards the deliberate attempt to retrieve a memory as an endogenous, top-down process. If scanning a crowd for one specific person is an example of an endogenous attentional task, then scanning one's memory for "where did I park the car today?" is an example of an endogenous AtM task. And just like a juggler in that crowd may capture attention away from the crowd search in an exogenous manner, memory of a previous day's fender-bender may capture attention away from the "where did I park the car today?" memory scan in an exogenous manner. A severe car accident - a truly traumatic memory - may capture attention much more forcefully, to the point where it becomes invasive. Furthermore, weaker memories - memories that we have to think about and struggle to retrieve - are by definition characterized by endogenous processing. A weak familiar or known (as opposed to a strong recollected or remembered), have-to-think-about-it memory is an endogenous phenomenon: attempting to recall a memory is itself a deliberately attention-demanding process. Thus, episodic memory recall can involve both endogenous

and exogenous processing. This is the "memory" aspect of the "Attention to Memory" (AtM) hypothesis.

There is evidence that this conceptual distinction is represented by a neuroanatomical distinction between dorsal and ventral posterior parietal cortex (Cabeza et al., 2008; Cabeza et al., 2011; Ciaramelli et al., 2008) and that switching between the two involves the dACC (Peelen, Heslenfeld & Theeuwes, 2004). Specifically, recall of weak/familiar/known memories activate a BOLD (blood oxygen level-dependent) response in the dorsal attentional system, in the more dorsal aspect of the intra-parietal cortex of the superior posterior parietal cortex Brodmann area 7 and the dorsal half of area 19.

In contrast, strong/recollected/remembered memories are considered part of the ventral (bottom-up) attentional system, represented by brain regions at the temporo-parietal junction, in the inferior posterior parietal cortex Brodmann areas 39 and 40. These are the same regions, activated during episodic memory recall, that become activated in top-down and bottom-up attentional tasks (Corbetta & Shulman, 2002). While both top-down attentional searches and top-down memory searches can still be considered endogenous, "goal-directed" or “deliberate” may better characterize the process. One distinction is that while bottom-up attention is considered exogenous, bottom-up episodic memory recall can be thought of as incoming rather than truly exogenous. The top-down vs. bottom-up distinction can be extended to other domains in cognition. For example, introspective thoughts can be framed as deliberate problem-solving

(pondering) vs. compulsive rumination (brooding; see Table 1).

TABLE 1

PSYCHOLOGICAL CONSTRUCT	TOP-TOWN	BOTTOM-UP	CITATION
Attention	Endogenous	Exogenous	
	Goal-driven	Stimulus-driven	Corbetta & Shulman, 2002
	Will	Attention	James, 1890
	Intention/ determination	Habit	Ach, 1910
	Controlled	Automatic	Atkinson & Shiffrin, 1968
Memory	Deliberate episodic recall	Proustian memory flooding	
	Deliberate trauma recall	Flashback	
Rumination	Pondering	Brooding	Joorman 2006; Whitmer & Gotlib 2011
	Experiential	Conceptual-evaluative	Kashdan 2012
	Active	Passive	

Terms used to describe top-down and bottom-up cognitive processes

While superior/dorsal parietal vs. inferior/ventral parietal cortex represents the distinction between top-down and bottom-up AtM, the initial need for the cognitive control that engages the dorsal attentional network is detected and triggered by the dACC. Thus, deficits in AtM-related processes may involve an inability to detect controllability (discussed below), to switch into top-down control, or to maintain such control.

II. IMPLICATIONS OF AtM FOR PTSD

A. SYMPTOMS, NEUROIMAGING, and THERAPY

The AtM hypothesis may have interesting and largely unexplored consequences for posttraumatic stress disorder (PTSD) in the domains of clinical manifestation and cognition, neuroimaging, and clinical therapy. The most influential psychological model of PTSD is the fear conditioning model (Jovanovic, Kazama, Bachevalier, & Davis, 2012; Orr et al., 2000; Pitman & Orr, 1986; VanElzakker et al., 2014) which has been enormously useful but is admittedly incomplete. For example, it does not explain ongoing concentration problems when no conditioned stimulus reminders are present. The AtM hypothesis may shed light on such symptoms, offer an explanation for why some existing forms of cognitive therapy may work, and provide researchers with new ideas for treatment. Importantly, the dorsal anterior cingulate cortex (dACC) is an important hub for both the fear conditioning model and for the AtM hypothesis.

BOX 1:

An insight from 125 years ago reflects the distinction revealed by modern neuroimaging techniques: the dual attentional systems discussed above. In his canonical book Principles of Psychology, William James described attention as "the taking of the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. ... It implies withdrawal from some things in order to deal effectively with others." The inability to withdraw from traumatic memories that defines the experience of PTSD renders sufferers unable to deal effectively with those other things that comprise a more normal and healthy life. According to the AtM hypothesis of PTSD, this at least partially reflects a failure to properly maintain top-down attention and resist bottom-up attentional capture by both external stimuli and from internal memories of trauma.

James went on to describe what we would now call exogenous

> attentional capture: "In involuntary attention of the immediate sensorial sort the stimulus is either a sense-impression, very intense, voluminous, or sudden; or it is an instinctive stimulus, a perception which, by reason of its nature rather than its mere force, appeals to some of our congenital impulses ... these stimuli differ from one animal to another, and what most of them are in man: strange things, moving things, wild animals, bright things, pretty things, metallic things, blows, blood, etc." When people with PTSD describe intrusive re-experiencing symptoms such as nightmares and flashbacks, they frequently describe the re-playing of moments that were "very intense, voluminous or sudden" and included "bright things... blows, blood..." (James, 1890).

In the AtM schema, the PTSD symptom of a flashback is a bottom-up, attention-capturing recollection taken to its most extreme. Evidence for this conceptualization is still mostly indirect and speculative. Referring to studies of healthy individuals, according to Moscovitch's group, "(it is) expected (to see) the IPL (inferior parietal lobe) to be consistently engaged when memory products are strongly experienced as targets, for example when individuals subjectively feel as if they are reliving their memories... when memories are strong, (and) accompanied by rich contextual details" (p. 1832, Ciaramelli et al., 2008). They describe bottom-up recollection as "a vivid, subjective feeling of reliving the original event" (p. 1829, Ciaramelli et al., 2008). In PTSD, despite lacking contextual completeness, traumatic flashbacks are characterized by a subjective feeling of reliving the original event, with intensely vivid episodic details including the same emotions experienced during the traumatic incident.

It may be the case that the brain "learns" especially during protracted periods of necessary hypervigilance and hyperarousal (such as repeated abuse or combat tours) that shifting attentional resources to the capture of bottom-up

stimuli is vital for personal safety and survival. However, when the abuse stops or the combat tour ends, the bottom-up processing becomes maladaptive and pathological. It may also be the case that, even before the traumatic experience, some individuals have a reduced ability to maintain cognitive control that renders them prone to bottom-up attentional or memory capture. The two possibilities - learned effects from trauma and pre-existing vulnerability - may also interact to produce PTSD symptoms. The dysfunction of attention-related structures in PTSD points to such a possibility. For example, the dACC is an important "switch" between bottom-up and top down as it is common to the "salience network" (Menon & Uddin 2010) which alerts to salient stimuli (bottom-up capture) and to the "frontoparietal control network" (Spreng, Sepulcre, Turner, Stevens, & Schacter, 2013) which maintains executive control and goal-directed cognition (top-down attention). In PTSD, studies consistently show hyperresponsivity in the dorsal anterior cingulate cortex across all manner of task (e.g., VanElzakker, Staples & Shin, in press) and even hyperactivity at rest (Shin et al., 2009). However, the presumed role of anterior cingulate cortex in PTSD symptoms is typically relegated to fear conditioning and extinction processes as opposed to loss of cognitive control. Therefore the relationship, or lack thereof, between dACC dysfunction in PTSD and propensity for exogenous attentional capture remains understudied. Simple studies of attentional capture using neutral stimuli could be a good starting point to elucidate these distinctions, and fMRI (functional magnetic resonance imaging) studies are a logical next step. The

current studies will work to this end.

Intense, realistic flashbacks triggered by "reminder" stimuli are certainly an important clinical manifestation of PTSD, but that is not the only symptom. Many individuals with PTSD talk about going through a period of social withdrawal, partially because of a sensation of sensory overload. For example, when a soldier first returns home from combat, completely neutral, non-combat-related stimuli can cause a sensation of being overwhelmed. They may feel inundated by the sounds, lights, and crowds of an otherwise-neutral place like a grocery store. Importantly for fear conditioning models, it is not the case that these symptoms are driven by overgeneralized conditioned stimuli (i.e., the grocery store is not filled with reminders of combat and yet still triggers symptoms). Hypervigilance and hyperarousal symptoms would inappropriately assign salience to neutral stimuli. This may be related to why it is difficult for individuals with PTSD to focus, read, or maintain concentration. The AtM hypothesis posits that such attention symptoms may also share a root cause with intrusive memories and thoughts.

Most PTSD neuroimaging work has essentially focused on fear-relevant neurocircuitry, especially anterior cingulate and other structures of the medial prefrontal cortex, hippocampus, and amygdala (e.g., Shin, Rauch, & Pitman, 2006; VanElzakker et al., 2014; Zoladz & Diamond, 2013). Furthermore, almost all of the existing PTSD neuroimaging literature has focused on negatively valanced emotional stimuli (e.g., Shin et al., 2006). Although there are a handful of PTSD neuroimaging studies that report parietal cortex abnormalities and a

handful of PTSD studies that utilize neutrally valenced stimuli (reviewed below), the functional imaging of parietal cortex during neutral stimuli tasks in PTSD remains largely unexplored. While structures such as the amygdala and dACC are clearly involved in learned fear, their roles in learned fear may be a subset of broader roles that relate to top-down vs. bottom-up processing as discussed below.

Exposure-based therapy for PTSD is based upon the fear conditioning model, and therapeutic recall of trauma is analogous to the extinction of conditioned fear. Interestingly, one could conceivably frame fear extinction recall as a top-down process, which must override a prepotent bottom-up conditioned fear response. In this conceptualization, even the fear conditioning model reflects bottom-up phenomena that capture attention to the detriment of top-down control. Conditioned fear seemingly sits at the intersection of attention and memory, with the stimulus itself and its associated memory capturing cognitive resources. More directly related, attentional training has emerged as a promising form of cognitive therapy for anxiety disorders (e.g., Amir et al., 2009; Schnyer et al., in press). The AtM hypothesis identifies a specific mechanism by which such training could help PTSD symptoms. According to the hypothesis, attention training exerts its effects not by training avoidance of trauma-related stimuli but by strengthening endogenous cognitive control and exercising the circuits that underlie such control.

B. EXISTING STUDIES

1. Attention Bias for Emotional Stimuli in PTSD

Given the assumption embedded in the DSM that attention and concentration problems in PTSD are directly related to the triggering trauma, much research has focused on the effects of emotional distractors. Neuroimaging studies utilizing emotional distractors in PTSD have shown reduced activation of parietal cortex and lateral prefrontal cortex (e.g. Blair et al., 2013; New et al., 2009; Pannu Hayes, Labar, Petty, Mccarthy, & Morey, 2009). These regions are part of the top-down circuitry described in the dual attentional systems account described by Corbetta & Shulman (2002). Thus, their dysfunction in PTSD may be evidence that distractibility by emotional cues may reflect a loss of top-down attentional control. Conversely, in a paradigm of emotional face-viewing (as opposed to active attention during distraction), Williams et al. (2006) reported increased BOLD response in superior and decreased BOLD response in inferior parietal cortex in PTSD relative to non-traumatized controls. These results may evidence increased need for effort during cognitive tasks requiring cognitive control.

While Blair et al. (2013) showed reduced recruitment of attentional neurocircuitry in individuals with PTSD compared to trauma-exposed and trauma-unexposed controls, their research also supports the idea that trauma-exposure per se may affect top-down attentional control. Trauma-exposed control participants who never developed PTSD showed increased activation in these

same top-down attention-associated dorsal regions compared to both PTSD and trauma-unexposed groups (Blair et al., 2013). More recently, White, Costanzo, Blair & Roy (2015) gave 57 combat veterans with subthreshold PTSD symptoms an emotional distraction task (emotional Stroop task). They found that increased PTSD symptoms were associated with increased fMRI BOLD responses in brain structures involved in top-down control, such as dACC and dorsolateral prefrontal cortex (DLPFC). These studies provide evidence that even subthreshold symptoms may affect attentional neurocircuitry. However, this result could be interpreted in different ways. For example, it could be that the increased activation reflects a pre-existing vulnerability factor that rendered those individuals more likely to experience PTSD symptoms after trauma. In this interpretation, one would expect the same trait to exist in a combat-unexposed identical twin. The increased activation in top-down circuitry would reflect ongoing effort due to existing weakness of the dorsal attentional and control systems. In those individuals with a pre-existing vulnerability of weak top-down control, the bottom up process "wins" and PTSD symptoms emerge upon exposure to a traumatic event. A competing interpretation is that increased activation could also reflect relatively increased efforts at control that became necessary after the emergence of PTSD symptoms. In this interpretation one would not expect the same trait to exist in a combat-unexposed identical twin. Such a scenario would suggest that trauma exposure causes strengthening of bottom-up capture which requires effortful cognitive control to harness. Our combat-discordant identical

twin cohort may clarify these potential interpretations (discussed below).

While the above research has been conducted using emotional distractors, the top-down attention system abnormalities may not necessarily be specific to emotional cues. A related hypothesis is that the attentional neurocircuitry abnormalities seen in PTSD render individuals with PTSD more prone to attentional capture by neutral-valence stimuli as well as trauma-related and emotional stimuli. In turn, such an abnormality could reflect an emergent property of PTSD symptomatology, or may reflect a familial vulnerability to PTSD that pre-dated trauma exposure. Deficits in sensory filtering (i.e., problems with suppressing irrelevant environmental sensory stimuli) have been self-reported in PTSD (Stewart & White, 2008). This was especially true in women with PTSD who were high in hypervigilance symptoms. According to our hypothesis, this may reflect a propensity for exogenous attentional capture at the expense of endogenous, goal-driven attention. Interestingly, in the Stewart et al. (2008) study these deficits were associated with PTSD diagnosis per se, and were not observed in multiple-trauma-exposed individuals without PTSD. This is evidence that such deficits reflect either an emergent property of PTSD or a familial vulnerability factor for PTSD, as opposed to an effect of trauma exposure.

2. Attention for Neutral Stimuli in PTSD

There are only a handful of studies that assess attention in PTSD using neutral-stimuli paradigms (reviewed in Aupperle, Melrose, Stein, & Paulus, 2012). For example, during visual search for a nonmatching shape, a salient (differently

colored) but non-emotional stimulus captured attention to an extent that was correlated with both depression and PTSD symptom severity (Esterman et al., 2013). Most neutral-stimulus studies in PTSD have assessed some combination of cognitive processes, as opposed to isolating attentional capture. Neutral stimuli studies of attention in PTSD are described here.

In one of the relatively few studies of PTSD using neutral stimuli, Horner et al. (2013) conducted a behavioral study that compared the performance of individuals with PTSD to "no diagnosis" controls on three neutral-stimuli executive function tasks (the Trail Making Task, the Digit Span Task, and the Mental Control task). The Trail Making Task is a neuropsychological test of visual attention and task switching that uses neutral stimuli. Horner et al. (2013) found that individuals with PTSD performed worse on the Trail Making Task than controls, even when controlling for task effort. There was no difference in Digit Span or Mental Control tasks, both of which are tests of executive function that also use neutral stimuli. However, the external validity of this study is limited by the fact that all participants - including controls - were recruited from a VA Medical Center's Neuropsychology Clinic. All participants were there due to referrals that were "typically made because of concerns on the part of the patient, family member, or healthcare provider about cognitive abilities" (p. 91, (Horner, Mintzer, Turner, Edmiston, & Brawman-Mintzer, 2013). Therefore, both the PTSD group and the control group suffered from selection bias towards cognitive dysfunction. Furthermore, this study did not report any data regarding trauma

exposure, and it is therefore unclear if any group differences were due to PTSD or to trauma exposure (i.e., it is unknown if controls were trauma-exposed or not). A study utilizing the same combat-discordant identical twin paradigm as the current study found that combat-exposed individuals with PTSD and their combat-unexposed twins shared deficits in executive functioning, evidencing such traits to be familial vulnerability factors (Gilbertson et al., 2006).

In auditory oddball tasks, participants must listen for target sounds while ignoring distractor sounds. In other words, they must engage in top-down attention while resisting bottom-up attentional capture. In an EEG (electroencephalogram) study, male military cadets varying in their trauma history participated in an auditory oddball task using emotionally neutral stimuli (sound effects such as computer-generated buzzes and whistles or auditory recordings of keys jangling; (Kimble, Fleming, Bandy, & Zambetti, 2010). The P300 ERP (event-related potential) component response to target and novel (distracting) stimuli was recorded, and the effects of trauma history (Trauma Experiences Questionnaire), PTSD symptoms (PTSD Symptom Scale; PSS), and dissociation (Dissociative Experience Scale; DES) were assessed. Approximately half (15 of 27) reported a trauma history that met DSM-IV criterion A. While trauma history predicted smaller P300s to target stimuli, PSS and DES scores did not. Trauma history also predicted smaller P300s to novel distracting stimuli. Smaller P300s to novel distracting stimuli were found in those participants with the highest dissociation. Given the P300 is considered to be an endogenous potential

(Polich, 2007) and is strongest in electrodes over the parietal cortex (Basar et al. 1984), this is evidence for weaker endogenous control after trauma exposure that is irrespective of PTSD symptoms and based in frontoparietal circuitry.

Another neutral-stimuli oddball task also used salient but non-trauma-related auditory tones (targets). Bryant et al. (2005) presented auditory targets pseudo-randomly in a sequence of distractor background tones, while participants were in an fMRI environment. They found greater amygdala and dACC responses in participants with PTSD relative to a non-traumatized control group. They also reported a positive correlation between level of amygdala activation and PTSD symptom severity (Bryant et al., 2005). A subsequent replication of this study by the same group added concurrent SCR (skin conductance response) to fMRI to compare 11 individuals with PTSD to 11 non-traumatized controls (Felmingham et al., 2009). They found that the target tones which elicited an SCR were associated with increased dACC and decreased subgenual anterior cingulate cortex (sgACC) activation in the PTSD group, relative to controls. These studies demonstrate that brain regions typically associated with fear conditioning and extinction abnormalities in PTSD were also associated with responses to neutral stimuli. However, because this study did not include trauma-exposed non-PTSD controls, it is unable to attribute the findings to PTSD versus trauma exposure. The experiments proposed herein address this important limitation.

The above studies observed attention-related abnormalities in the "usual

suspect" brain regions such as amygdala and ventromedial prefrontal cortex, as well as in the dACC. There is other evidence that brain regions implicated in fronto-parietal attentional process are disordered in PTSD. The sparse literature utilizing emotionally neutral stimuli point to possible mechanistic reasons for this clinical manifestation. For example, activity in medial frontal gyrus, part of the dorsal frontoparietal attention circuit, is inversely correlated with PTSD symptom severity, not only for emotional distractors, but also for neutral distractors (Pannu Hayes et al., 2009). In other words, loss of control over bottom-up capture is associated with PTSD. Even for neutral stimuli, decreased top-down dorsal attentional system activity in PTSD patients correlates with worse symptoms. The implication is that, in PTSD, there is an overall biasing towards bottom-up processing and attentional capture, whether that attention is to external or internal (memory or rumination) cues. A study of executive function showed reduced dorsolateral prefrontal cortex (DLPFC) and increased superior parietal cortex activation during working memory updating in PTSD relative to control (Clark et al., 2003).

III. CURRENT STUDIES: BACKGROUND & HYPOTHESES

A. PARTICIPANTS

The current proposal includes two experimental paradigms and two distinct participant samples. While most research addressing the "problems with

concentration" diagnostic criterion has used trauma-related emotional stimuli, the proposed research will use the Posner Cueing Task and the MSIT, which present emotionally neutral stimuli (e.g., boxes, arrows, stars, and numerals).

The Posner Cueing Task will include Vietnam War combat veterans and their combat-unexposed identical twins, as well as a separate cohort of undergraduates with varying levels of trauma history. The MSIT task will include the Vietnam twin participants only. Here, I will briefly describe the latter participant group and its relevance.

1. Twin Cohort

An important issue in PTSD research is the origin of any cognitive abnormality seen in individuals with PTSD. Such an abnormality may reflect 1) an emergent property of PTSD symptomatology, 2) a symptom of trauma exposure per se that does not necessarily reflect PTSD diagnosis, or 3) a trait that reflects a vulnerability to PTSD. While the most likely explanation for such a vulnerability trait is that it pre-dated the trauma exposure and subsequent PTSD diagnosis, without having tested the twins pre-trauma, we remain unable to state definitively whether any shared abnormality pre-dated trauma exposure as the twins may have shared environments both before and after trauma exposure. Nevertheless, our combat-discordant twin cohort allows for inferences about the origin of any abnormality (Gilbertson et al., 2010; True et al., 1993). This cohort includes 27 Vietnam War combat veterans, each of whom has a combat-unexposed identical (monozygotic) twin. Slightly less than half (n=11) of the combat-exposed

individuals have a current PTSD diagnosis. The remainder of combat-exposed individuals do not have a current PTSD diagnosis. None of the combat-unexposed co-twins have PTSD.

Thus, there are 4 groups of individuals: ExP+, UxP+, ExP-, and UxP-.

Ex = combat exposed

Ux = combat unexposed (no Ux twin has PTSD)

P+ = member of a twin pair including an Ex twin with PTSD

P- = member of a twin pair including an Ex twin without PTSD (neither twin has PTSD)

Therefore, ExP+ and UxP+ are brothers; ExP- and UxP- are brothers. Note that only one group, ExP+, has a diagnosis of PTSD. The co-twins of ExP+ individuals are UxP+ and do not have PTSD despite the P+ designation. ExP- individuals have been in combat but do not have current PTSD. The co-twins of ExP- individuals are UxP-. The remainder of the text will use this nomenclature.

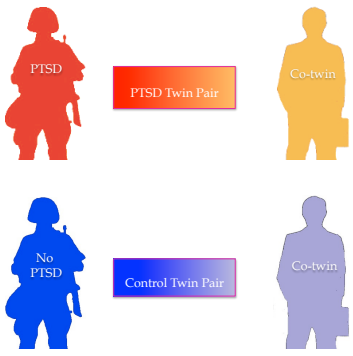


FIGURE 1 , Credit to Reid Offringa for creating this figure
Red = ExP+, yellow = UxP+;
blue = ExP-, violet = UxP-

Statistical analyses of variance among these four groups are generally accomplished using a 2x2 mixed-model ANOVA. The *main effect of diagnosis* refers to the PTSD diagnosis of the combat-exposed twin (P+ vs. P- pairs) and is treated as a between-subjects variable. A main effect of diagnosis implies a vulnerability or resilience factor that is shared between brothers. The *main effect of combat exposure* (Ex vs. Ux) is treated as a within-subjects variable because the difference in combat exposure is between co-twins. A main effect of exposure implies an effect of trauma per se. A diagnosis x exposure interaction such that the ExP+ group differs from all other groups implies an emergent property of PTSD.

The twin cohort was mostly recruited from the US Veterans Administration (VA) Vietnam Era Twin Registry (VETR) (Henderson et al., 1990). Two twin pairs were recruited from advertising or the University of Washington's Twin Registry (UWTR). Those two pairs were younger than the average Vietnam veteran (mid-40s). One of those pairs was P+ and the other was P-. The P+ pair's Ex twin had PTSD related to an accident, and the P- pair's Ex twin had trauma related to the first Gulf War (1991). After genetic testing, it was discovered that one Vietnam veteran P- pair was actually dizygotic. Due to the low N, this pair was included in most analyses, but one member of this pair also had failed MSIT behavioral data and therefore they were excluded from MSIT behavioral analyses. The Partners Healthcare IRB and VETR IRB approved all procedures in the studies involving twin participants, and participants provided written informed consent.

2. Undergraduate Cohort

Because it includes participants with varying levels of trauma history, the undergraduate cohort allows investigation into the relative contribution of trauma exposure to abnormalities in attention. This is important because, as previously noted, there is some evidence that attentional processes are affected by trauma exposure even in the absence of PTSD diagnosis. While the twin cohort is all male and mostly approximately 60 years of age, the external validity of these studies is helped by the fact that the undergraduate cohort includes both sexes and is mostly 18-20 years of age. Data from 42 undergraduates will be included. Participants were recruited though undergraduate psychology courses at Tufts University, and were given class credit for completing the experiment. Tufts' IRB approved all experimental procedures involving this cohort, and participants provided written informed consent.

B. PARADIGMS

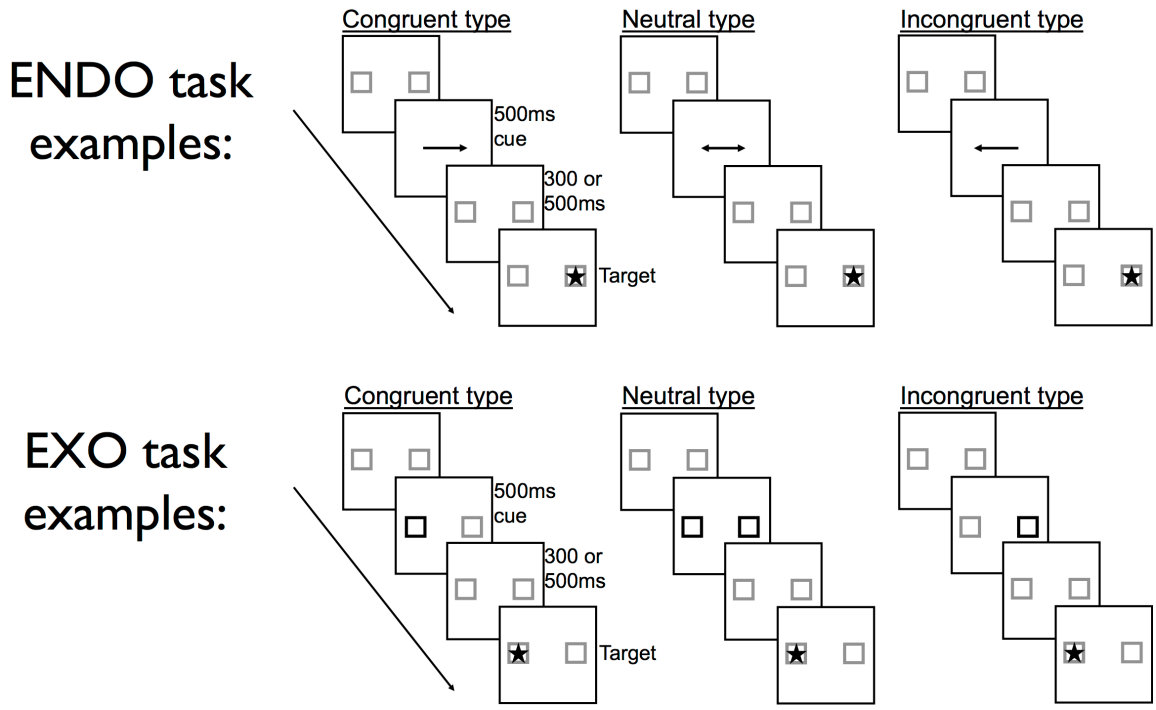
1. Posner Cueing Task Paradigm

Cognitive psychologist Michael Posner's influential theories of attention began over 30 years ago with behavioral paradigms and continue to be validated by modern functional neuroimaging techniques. Posner's theories on spatial attention purport that attention is like a spotlight that can be directed towards one area of visual space. Even when deliberately focused on a singular point, a directional cue can prime that spotlight towards a different area of visual space.

This priming can occur via either a top-down cue presented at the current area of focus, like an arrow suggesting directionality, or a bottom-up cue presented at the intended area of focus, like a flash of light. Posner developed a simple cueing task to demonstrate that attention can be captured by directional priming (Posner, 1980). The current research uses this Posner Cueing Task paradigm to begin the process of understanding how top-down and bottom-up processes are germane to the mechanisms of psychological trauma and PTSD.

In these tasks, participants look at a fixation point in the middle of a computer screen, which is flanked to the left or to the right by square boxes. Participants respond by pressing the space bar as quickly as they can when the target, a star, appears inside one of the two boxes.

FIGURE 2



Posner Cueing Task, ENDO and EXO versions. Not shown are lure trials in which no target (star) appears. Image adapted without permission from Wikipedia commons.

Drawing attention to one side or the other affects response time, depending on whether the cue and target are in the congruent location. There are two versions of the task, here called ENDO (for endogenous attention) and EXO (for exogenous attention), which describe the directional cue. In both the ENDO and EXO versions, there will be neutral trials in which attention is cued equally to both sides, as well as lure trials in which there is no target. In *congruent* trials, a cue directs the spatial attention "spotlight" to the box in which the target will appear. This covert cueing will cause the response time to be faster in proportion to how well the cue worked. In the *incongruent* condition where attention has been drawn away from the target, the response time to target will be slower in proportion to how well the cue worked. The extent to which an individual is more

prone to exogenous attentional capture vs. endogenous attention can be calculated by subtracting congruent trial response times from incongruent trials response times within both ENDO and EXO tasks. Propensity for exogenous attentional capture would mean greater difference scores in the EXO but not the ENDO task. Lure trials (i.e., no target) are included in both the ENDO and EXO tasks. Along with exogenous attentional capture, the propensity to respond inappropriately to lure trials is hypothesized to be a proxy for PTSD hyperarousal symptoms.

Stimuli were presented on a Macintosh computer using MacStim v3, and participants were instructed to press the space bar when the target appeared. Stimulus onset asynchrony varied; target appeared either 300msec or 500msec after cue. Both the undergraduate and the twin cohorts performed the ENDO and EXO components of the Posner Cueing Tasks, and a simple baseline response time task that could be used to check for group differences in response time. In the ENDO task, the fixation point is briefly (500ms) replaced by one of 3 cues: an arrow to the left, and arrow to the right, or a double-headed arrow. Either 300ms or 500ms after the cue, the target star appears. The arrow is an endogenous cue that compels participants to covertly orient attention to a position in visual space other than fixation (i.e., to the box on the left of the screen or to the box on the right of the screen). It is considered endogenous because an arrow is a symbol of a goal-directed behavior, and it is presented at the fixation point as opposed to where the target will be. This is in contrast to exogenous cues shown in the EXO

version of the task that are presented away from the fixation point in the peripheral visual field, and are visually salient by being bright. In the EXO task, one of the two boxes brightens. The brightening cue serves as a stimulus-driven form of exogenous attentional capture because it pulls attention to one side of the screen or the other. In the congruent condition, the brightening cue will be in the same location as the target.

In addition, to the Posner Cueing Task, both cohorts completed several psychometrics (see Table 2). These include the Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Traumatic Life Events Questionnaire (TLEQ), and Clinician Administered PTSD Scale (CAPS) for DSM-IV. Basic demographic information about all participants was also obtained. The psychometrics allow the quantification of anxiety, depression, psychological trauma, and PTSD symptoms. Based upon preliminary analyses and previous research discussed above, I hypothesized that trauma history (TLEQ score) will significantly explain the difference between ENDO and EXO response times. However, in most dACC-related tasks one would have expected a main effect of diagnosis.

TABLE 2

	Both Cohorts	Combat Discordant Twins only	Undergraduates only
Paradigm	Posner Cueing Task	MSIT behavioral task	
	-ENDO cues	-MSIT fMRI	
	-EXO cues	-MSIT SCR	
	-Baseline response times		
Psychometrics	Beck Anxiety Inventory	Barratt Impulsiveness Scale	Ruminative Responses Scale
	Beck Depression Inventory	Childhood Trauma Questionnaire	Attentional Control Scale
	TLEQ	Michigan Alcohol Screening Test	
	CAPS	Wender Utah Rating Scale	
	Basic demographic & medical info	Risk Attitude Scale	
	Revised NEO inventory	Sensation Seeking Scale	
		Rivermead Post-Concussion Symptoms Questionnaire	
		VA/DoD Structured Interview for Collection of Head Trauma Event Characteristics	
		Positive and Negative Affect Schedule (PANAS)	
Other Data		fMRI tasks and resting state	
		MRI structural & spectroscopy	
		Genetic and epigenetic data	
		Neuroendocrine data	

Aspects of the experiments performed by both participant cohorts, twins only, or undergraduates only.

2. Multi-Source Interference Task (MSIT)

The MSIT is a motor task made challenging by interference from a prepotent response. In this task, participants place 3 fingers on three different buttons

representing the numerals 1, 2, and 3. They are presented with sequential trials of three-numeral combinations. The task is to press the button that corresponds to the identity of the numeral that is different from the others. This is easy during non-interference trials (Control condition) when the identity of the different numeral matches its position on the button box. The challenge comes during interference trials (Interference condition) when the identity of the different numeral does not match its position on the button box. The control trials are also easier because their matching numerals are always zeros.

Control condition examples:

100 The 1 is the different numeral, so press button 1. Non-interference control because it is also in the first position.

020 The 2 is the different numeral, so press button 2. Non-interference control because it is also in the second position.

003 The 3 is the different numeral, so press button 3. Non-interference control because it is also in the third position.

Interference condition examples:

313 The 1 is the different numeral, so press button 1. Interference because it is not in the first position.

112 The 2 is the different numeral, so press button 2. Interference because it is not in the second position.

322 The 3 is the different numeral, so press button 3. Interference because it is not in the third position.

FMRI studies have revealed that the MSIT task reliably activates regions of the dorsal attentional network such as superior parietal cortex and dACC (Bush & Shin, 2006; Bush, Shin, Holmes, Rosen, & Vogt, 2003). There is some controversy regarding the particular physiological process that fMRI BOLD responses represent; therefore, direct measures are an important form of replication in studies utilizing fMRI. Sheth et al. (2012) used direct neuronal recording of patients undergoing cingulotomy to demonstrate dACC responsiveness during the MSIT task (Sheth et al., 2012). While the dorsal attentional network is involved in top-down control of visual attention, the cingulo-frontal-parietal cognitive/attention network engages when interference must be resolved. The intersection of interference resolution and top-down attention is likely where the Posner Cueing Task and the MSIT task overlap.

The dorsal anterior cingulate cortex (dACC) has several functions, one of which is to "boost" attention towards relevant cues when interference from distraction must be resolved (Weissman, Gopalakrishnan, Hazlett, & Woldorff, 2005). Interestingly, the dACC is also involved in learned fear and is hyperactivated in PTSD during a wide array of tasks (reviewed in Hughes & Shin, 2011; VanElzakker et al., 2014). A previous twin study revealed that the MSIT task activates the dACC of individuals with combat-related PTSD and their

combat-unexposed co-twins to a greater extent than combat-exposed individuals without PTSD and their combat-unexposed co-twins (Shin et al., 2011). This suggests that dACC hyperactivation represents a familial vulnerability factor for PTSD. The current study seeks to replicate Shin et al. (2011) while adding concurrent skin conductance response (SCR) as a measure of autonomic arousal. Shin et al. (2011) only acquired functional images from the front half of the brain, in order to target the anterior cingulate cortex. In the present study, we obtained functional images from the whole brain, allowing ascertainment of the role, if any, of the parietal cortex during the performance of this task in PTSD. Furthermore, MSIT data can be correlated with Posner Cueing Task data and a large aggregate of other data including functional and structural neuroimaging, psychometric, behavioral, neuroendocrine, and genetic data. We expect dACC activation to be correlated with response time difference scores (Interference minus Control conditions) in the EXO Posner task, and expect to see main effects of diagnosis for both the fMRI and behavioral dependent variables.

As mentioned earlier, resting-state fMRI studies have revealed that the dACC is part of a "frontoparietal control system" that may help to "switch" from top-down attention to bottom-up attention and memory (Vincent et al., 2008). Functional MRI studies have supported this, providing evidence of dACC involvement in shifts between endogenous and exogenous attentional systems (Peelen, Heslenfeld, & Theeuwes, 2004). Therefore, given the arguments made by the AtM hypothesis of PTSD, dACC dysfunction in PTSD may be an important

factor in the failure to maintain top-down attention and resist bottom-up distraction from both external cues and traumatic memories. The current studies allow direct testing of that hypothesis; for example testing the correlation between dACC activation in the MSIT and difference scores in the Posner Cueing Task. Interference MSIT trials require top-down control and therefore the MSIT interference vs. control BOLD contrast should offer a neural representation of top-down effort, while the EXO Posner Cueing Task can quantify the propensity for exogenous attentional capture.

C. USING the TWO PARADIGMS to TEST the AtM HYPOTHESIS of PTSD

The AtM hypothesis comprises top-down (endogenous) and bottom-up (exogenous) components, which are functionally related but still distinct, as evidenced by distinct neurocircuitry. The AtM hypothesis of PTSD posits that, with ongoing trauma exposure, individuals become hypervigilant as they learn to expect danger in their environment. This causes Hebbian learning (synaptic plasticity) in ventral circuitry, aided by glucocorticoid effects on synaptic excitability and synapse strengthening. One would expect this to be a particularly important mechanism for ongoing or recurrent trauma exposure of a type in which danger is a constant threat (i.e., repeated abuse or combat tours, as opposed to a single car accident in an otherwise danger-free life). While transient mild threat can facilitate cognitive control (Birk, Dennis, Shin & Urry, 2011), ongoing traumatic stress can place one on the other side of the Yerkes-Dodson

curve (Yerkes & Dodson, 1908). The amygdala becomes hyper-responsive as ongoing danger causes the brain's conception of "salient" to expand, whereby otherwise neutral stimuli will capture attention. Thus, attentional capture becomes driven by the bottom-up ventral attentional system. Individuals with a particularly strong top-down dorsal attentional system will be able to compensate and maintain cognitive control in the face of distractors, and will be relatively resilient to PTSD. Individuals with a weaker dorsal attentional system will too easily switch from top down control to bottom-up capture, and this will generalize to attention, memory, and introspective thoughts (rumination). Increased functional activation of dorsal attention network structures may reflect the exertion of greater-than-normal effort. In this conception, "problems with concentration" in PTSD represent the interaction of learned hypervigilance with a pre-existing vulnerability in the form of weak top-down cognitive control.

D. HYPOTHESES

1) Posner Cueing Task (twin cohort): Based upon preliminary data analysis, there will be a significant interaction between diagnosis and trauma exposure on the propensity for exogenous attentional capture, but not on endogenous attentional priming.

2) Posner Cueing Task (twin cohort): Exogenous attentional capture will be significantly correlated with CAPS-D hyperarousal symptoms in

combat-exposed individuals.

3) Posner Cueing Task (twin cohort): Errors of commission (i.e., responses to lure trials) will produce the same ANOVA results as exogenous attention capture and will also be positively correlated with hyperarousal symptoms in combat-exposed individuals.

4) Posner Cueing Task (undergraduate cohort): The propensity for exogenous attentional capture will be positively correlated with CAPS-D score among those individuals with PTSD symptoms, and positively correlated with trauma exposure (TLEQ scale score) in the general cohort.

5) MSIT task (twin cohort only): Based upon prior findings (Shin et al. 2011), individuals with PTSD and their co-twins (ExP+ and UxP+) will show greater dACC BOLD activation in the Interference vs. Control contrast than combat controls and their co-twins (ExP- and UxP-). In other words, there will be a main effect of diagnosis.

6) MSIT task (twin cohort only): Based upon prior findings (Shin et al. 2011), in combat-exposed individuals (Ex), dACC activation will be positively correlated with their own PTSD symptom severity. Ux BOLD response will also be correlated with symptom severity of the Ex cotwin.

7) MSIT task (twin cohort only): dACC activation to the Interference vs. Control contrast will be positively correlated with SCR magnitude across all participants.

8) MSIT task (twin cohort only): There will be a main effect of exposure on superior parietal cortex and DLPFC (dorsolateral prefrontal cortex) BOLD activation in the Interference vs. Control contrast.

9) MSIT task (twin cohort only): dACC activation to the Interference vs. Control contrast will be positively correlated with MSIT response times (I minus C difference scores) across all participants.

10) Twin cohort: MSIT task dACC activation to the Interference vs. Control contrast in the PTSD group (ExP+), will be positively correlated with Posner Cueing Task propensity for exogenous attentional capture.

IV. CURRENT STUDIES: DATA ANALYSIS & RESULTS

A. DATA ANALYSIS for the POSNER TASK

Posner Cueing Task data for both the twin and the undergraduate cohorts were analyzed in the following fashion. First, errors of commission and omission were

recorded by respectively counting responses during lure trials and non-responses during cue trials. Lure trials were then excluded from further analyses. Next, non-responses and any trial with a response time faster than or equal to 0.1sec (100msec) were excluded. Because of the non-normal and positive distribution of response time data, all remaining response times were then natural log-transformed. After transformation, the primary dependent measure for both the EXO and ENDO tasks were Incongruent-Congruent difference scores. If attention is being captured, incongruent should be greater than congruent. If bottom-up, but not top down, attention is being captured, then the difference score should be significant for the EXO task but not the ENDO task. Thus the primary a priori dependent variable was a measure of exogenous attentional capture referred to herein as EXO-LOG (log response time difference between incongruent and congruent cues). A similar variable was calculated for the ENDO task (ENDO-LOG).

Given the circadian variance in response times (reviewed in Blatter & Cajochen, 2007; Valdez, Ramírez, & García, 2012), all participants from the twin cohort were tested in the morning, between 7:30am and 10:00am. This was not feasible in the undergraduate cohort.

B. POSNER TASK RESULTS: TWINS

The twin component of the Posner cueing task included 15 P+ pairs and 18 P- pairs (66 total individuals). Demographic and psychometric data are reported in

Supplemental Data, Table 3. An independent samples t-test revealed that the groups were matched for age, with P+ (M=60.91, SD=6.66) and P- (M=62.69, SD=3.74), t(31)=.65, *p*=.52. A one-way ANOVA revealed that the four groups were matched for years of education with ExP+ (M=13.81, SD=3.00), UxP+ (M=14.00, SD=3.97), ExP- (M=15.34, SD=3.63), UxP- (M=14.63, SD=2.73), F(3,62)=1.25, *p*=.30. One ExP+ individual (with PTSD) had severe sleep problems and was unable to stay awake to complete the EXO version of the task, and therefore his data and those of his cotwin were excluded from EXO analyses.

Data from our sample of combat-discordant identical twin pairs were subjected to a 2x2 mixed-model ANOVA with combat exposure as the within-subjects factor and PTSD diagnosis of the exposed twin as the between-groups factor (i.e., brothers are treated as a repeated measure with or without combat and the degrees of freedom reflect twin pairs, not individuals). The primary result from this study is a main effect of diagnosis on the EXO-LOG measure of exogenous attentional capture, F(1,30)=9.07, *p*=.005, eta^2= .23.

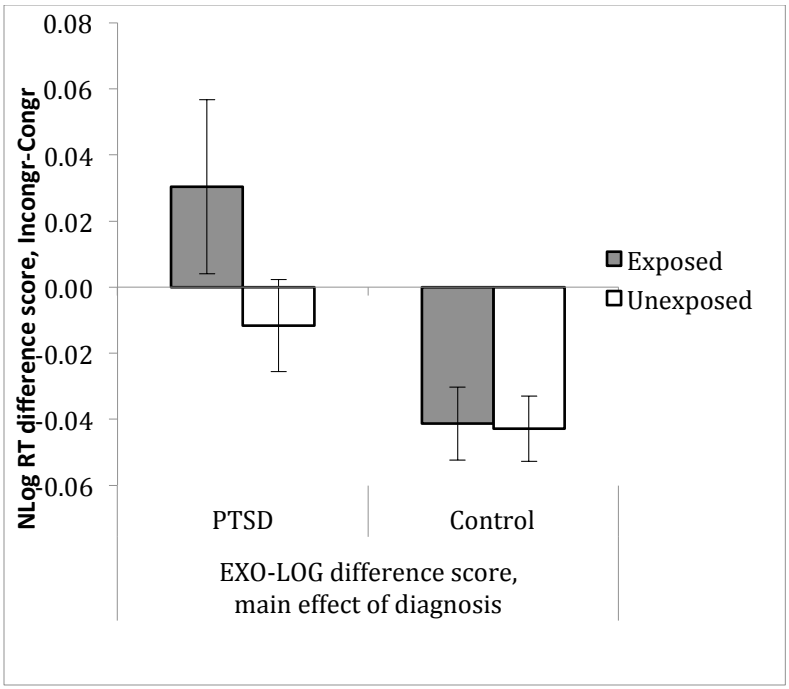


Figure 3. Main effect of diagnosis on EXO-LOG exogenous attentional capture. Main effect of exposure and the diagnosis x exposure interaction were not significant, *p*s>.30

We hypothesized propensity for exogenous attentional capture to be a proxy for the PTSD symptom of hyperarousal (Hypothesis 2). This was borne by a significant correlation between Ex participants' EXO-LOG score (incongruent minus congruent) and their own CAPS-D (hyperarousal subscale) score, r(32)=.53, *p*=.001. Any behavioral trait that reflects a familial vulnerability factor should also be present in the unexposed twins and should correlate with the symptom severity of the combat-exposed cotwins. There was a significant correlation between Ux EXO-LOG score (incongruent minus congruent) and corresponding Ex CAPS-D (hyperarousal subscale) score, r(32)=.52, *p*=.001(see Figure 4).

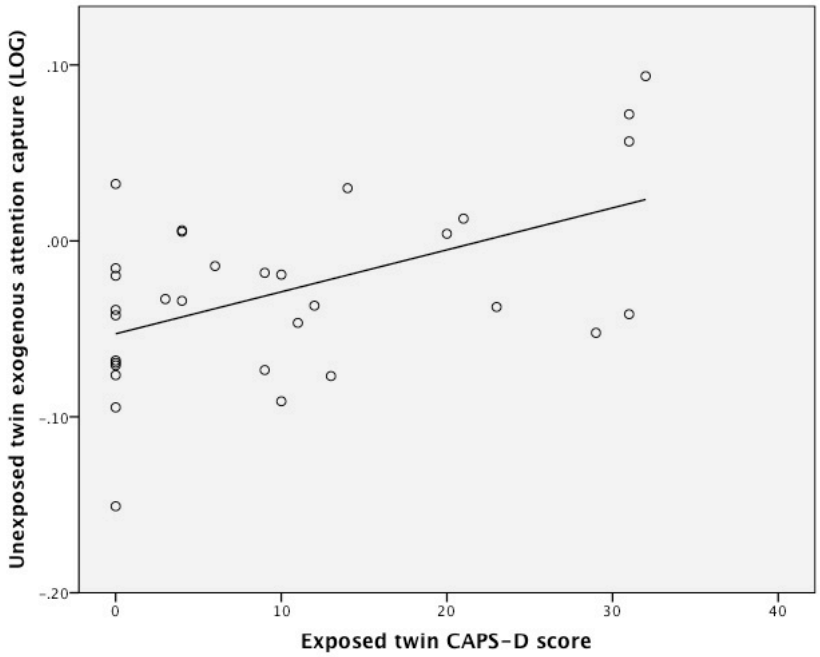


Figure 4 representing the a priori hypothesized significant correlation between exogenous attentional capture in combat-unexposed individuals and PTSD hyperarousal symptoms in their combat-exposed identical twins, r(32)=.52, *p*=.001 one-tailed.

The above results show main effects of diagnosis on exogenous task dependent measures. This was slightly different than our hypothesis (Hypothesis 1), which predicted an interaction between diagnosis and combat exposure. While the bar graph appears to reflect such an interaction, it was not significant, F(1,30)=0.415, *p*=.52. In accord with our hypothesis, there were no significant effects in the endogenous task. This effect was robust enough to survive several alternate methods of data cleaning (see Supplemental Data, Table 4).

Another predicted measure of hyperarousal (Hypothesis 3), there was also a significant main effect of diagnosis on errors of commission (responding to lure trials) across ENDO and EXO trials, F(1,31)=6.44, *p*=.016. ExP+ individuals

(M=4.13, SD=6.91) and UxP+ individuals (M=2.47, SD=4.88) committed more errors of commission than did ExP- individuals (M=0.72, SD=1.07) and UxP- individuals (M=0.56, SD=1.42).

C. POSNER TASK RESULTS: UNDERGRADUATES

There were no natural hypothesis-relevant categorical groups among the 42 participants in the undergraduate cohort (23 female). Therefore, most of our planned analyses did not include group-comparison statistics but rather correlational and regression analyses. In addition to relatively random sampling from the Tufts University Introduction to Psychology participant pool, we also used the following pre-screen questionnaire items to make our study visible to only certain students:

1) *Have you ever experienced or witnessed an extremely traumatic event that involved actual or threatened death or serious injury?*

2) *If you have experienced or witnessed an extremely traumatic event, do you: have recurring and intrusive distressing memories of the event AND do you spend a significant amount of effort avoiding any and all reminders of the event AND are you now more anxious and vigilant than you were before the event? Only answer YES if all of the above are true.*

Question 1 allowed us to prescreen for trauma exposure and question 2 allowed us to prescreen for PTSD symptoms. Therefore, we were able to gain a non-

representative sample with a higher concentration of trauma and PTSD symptoms than the general student population. While we did not make a categorical PTSD diagnosis, 6 students had a current CAPS score of 30 or higher, and 14 had a lifetime CAPS score of 30 or higher. On the other side of the spectrum, 19 students had a current total CAPS score of zero, and 17 had a lifetime total CAPS score of zero (this usually reflects a lack of Criterion A traumatic experience).

A table of one-tailed correlations failed to reveal any relationship between trauma exposure, symptom severity or other clinical variables and EXO-LOG scores (all *p*s>.18). Using partial correlation, adjusting for age, BDI, BAI, and RRS (rumination scale), there was not a significant correlation between current CAPS-D and EXO-LOG score (p>.38). The only clinical or demographic variable to correlate with EXO-LOG was a trend for age, r(32)=.34, *p*=.06.

D. LIMITATIONS of the UNDERGRADUATE STUDY

There are several limitations to the undergraduate study, including threats to internal and external validity.

Given the academic setting of recruitment, it is likely that participants in the undergraduate cohort had a higher average IQ than the twin cohort. While relatively higher IQ predicts lower PTSD severity (Macklin et al., 1998; McNally & Shin, 1995), it is also likely to predict global functioning even when controlling for PTSD severity. Thus, an undergraduate at Tufts with a CAPS score of 75 may

have less severe cognitive symptoms than a Vietnam veteran with a CAPS score of 75. Indeed, given that IQ tests are largely tests of executive function and that cognitive control is an expression of executive function, it may be important to parse that portion of variance in exogenous attentional capture-as-vulnerability to PTSD that is not simply explained by variance in IQ. Furthermore, there may have been differences in motivation between the two cohorts. In general, the twin cohort was highly motivated and attentive. Undergraduate participants are, at least anecdotally, considered by some experimenters to be somewhat less motivated.

The undergraduate academic setting may be important for another reason: age. While both undergraduate and twin cohorts have relatively homogenous age samples, the variance in age in the undergraduate cohort occurred during adolescent neurodevelopment (mean undergraduate = 19.13 years, SD=1.13). In the initial exploratory Pearson's correlation table, the only demographic or psychometric correlate of EXO-LOG that approached significance was age. The adolescent years are marked by the development of cognitive control (Steinberg, Cauffman, Woolard, Graham, & Banich, 2009). Even so, this was a trend-level non-a priori correlation, uncorrected for multiple comparisons, and therefore should be viewed with skepticism.

Another potentially important distinction between the twin cohort and the undergraduate cohort is the relatively homogenous traumatic experiences in the twin cohort. Unlike the twin cohort, in which all but one participant with PTSD had

combat-related Criterion A trauma, the undergraduate cohort had a wide variety of traumatic experiences. As discussed earlier, the "learning" of exogenous attentional capture is expected when traumatic events occur within the context of sustained hyperarousal and hypervigilance (such as the specific traumatic events that punctuate a year-long combat tour). While the twin cohort showed a main effect of diagnosis and not a combat x diagnosis interaction, the pattern of results alludes to greater attentional capture in ExP+ than UxP+ individuals. Perhaps importantly, any traumatic experiences among the undergraduate cohort were by definition childhood or adolescent traumas.

In the a priori analyses, undergraduate participants were not split into categorical groups based upon PTSD diagnosis, but some of the participants likely met criteria for current PTSD. PTSD symptom severity scores were recorded using the CAPS (Clinician-Administered PTSD Scale; Blake et al. 1995). Several types of analyses were attempted, including splitting participants into <30 CAPS score and >30 CAPS score, and removing all participants with a CAPS score of zero. None of those iterations returned significant a priori results. Despite the fact that CAPS was a primary dependent measure for the study, there are several critiques that arise from its use. In some cases, there appear to have been problems with CAPS question validity among some undergraduate participants. It may have been difficult for students to discuss personal and traumatic experiences with a perceived peer. For example, one student answered "yes" to both prescreen questions, but during the CAPS interview

denied having experienced a psychologically traumatic event or having any PTSD symptoms (CAPS score of 0). This student also answered 0 for other psychometrics, scoring zero or close to zero on the CAPS, Beck Depression Inventory, and Beck Anxiety Inventory. In at least one other instance, it seemed to be the case that a female participant was not comfortable discussing sexual abuse-related trauma.

The young age of the undergraduate participants (M=19.13, SD=1.13) also presented a problem with some CAPS items. If a participant reported a traumatic experience, it likely occurred when the participant was a child or adolescent. The CAPS is worded around changes that are related to the traumatic experience, but participants frequently struggled to answer questions (e.g., *"Yes, of course I no longer enjoy the same activities that I did before the trauma, I was 7 and I used to play with dolls"*). The CAPS-CA (Clinician-Administered PTSD Scale for Children and Adolescents) is written for interviewing actual children as opposed to interviewing young adults about childhood experiences. The TLEQ (Traumatic Life Events Questionnaire) was included, but only scores the actual experiences and not psychiatric symptoms. In retrospect, a more childhood-experience-specific psychometric should have been included because wording in the adult CAPS was frequently not appropriate.

My view of the CAPS, and especially of Criterion A (qualifying traumatic event), evolved through the course of the study. Initially, I followed the CAPS

script strictly: if a participant did not qualify for Criterion A, including the subjective experience of fear, helplessness, or horror (Criterion A2 of the DSM-IV version of the CAPS), that participant received a score of zero. With continued experience I grew critical of Criterion A and began to think that to require such specific peritrauma emotional experiences did not contribute to diagnostic validity. Many participants were clearly affected long-term by a particular experience, but did not report having those particular reactions during the triggering trauma. Feeling numb, excited, confused or even somewhat indifferent did not seem to correlate with other PTSD symptoms after the fact. As the study progressed, I decided to no longer end the CAPS interview if Criterion A was not met. This is another likely source of variability in the data. Interestingly, as I was beginning to have doubts, a debate about Criterion A was percolating in the PTSD literature, finally culminating in the removal of Criterion A2 in the DSM-V (Brewin, Lanius, Novac, Schnyder, & Galea, 2009; Brewin, Andrews, & Rose, 2000; Kubany, Ralston, & Hill, 2010). A newer version of the CAPS was released during the course of the study (Weathers et al. 2013), however for consistency and comparability the entire study was conducted with the older version.

Additional variability to the data may have resulted from using more than one experimenter. In fact at least six undergraduates, fellow graduate students or RAs ran participants including taking CAPS interviews. Thus, it is quite likely that some of the variance in CAPS scores would be explained by lack of consistency among interviewers. Three undergraduate participants returned lifetime CAPS

scores of 95, 112, and 117, indicating very severe PTSD symptoms. Current CAPS scores for some undergraduate participants also included scores of 78 and 82 - for comparison, the highest current CAPS scores among Vietnam veterans in the twin cohort were 85, 89, and 91. Some of the traumatic experiences of undergraduate participants were truly horrific and all undergraduates and RAs were trained; however, in all cases the CAPS with the highest scores were among the first CAPS the research assistants had ever administered. In contrast, for the twin study, one PhD-level psychologist with decades of assessment experience conducted all CAPS interviews.

Lastly, and likely explaining only a very small amount of variance, despite circadian variance in attention task response times (Valdez, Ramirez & Garcia 2012), time of day of testing was not kept consistent across participants.

E. MSIT TASK METHODS & DATA ANALYSIS

The MSIT task was performed during fMRI. We used a Siemens 3T high-speed echo-planar imaging (EPI) scanner with a 12-channel head coil. Participants lay supine in the scanner, with their head gently immobilized by pillows within the coil. All participants were vision-tested to ensure they could see the stimuli and if needed, participants were given MRI-safe glasses with lenses matching their vision correction prescription. Attached to the head coil was a tilted mirror allowing participants to view stimuli, projected onto a screen using MacStim v3 on a Macintosh Powerbook computer. All participants were allowed to practice

the task upon first entering the scanner, until demonstrating that they could perform the task; hence, amount of practice varied across participants.

First, after an automated scout and shimming, high-resolution structural MRI images were collected with a 3D MPRAGE sequence (TR=7.25msec, TE=3ms, flip angle=7°, 1x1mm in plane x 1.3mm). This allowed for spatial normalization and positioning for the subsequent scans. Scans using T1 (TR=8sec, TE=39msec, flip angle=90°) and T2 (TR=10sec, TE=48msec, flip angle=120°) sequences then were used for spatial registration of individual functional data. The functional scan was acquired using a T2*-weighted sequence (TR=1.5sec, TE=30msec, flip angle=90°). T1, T2, and functional image slices were all the same thickness (5mm, 1mm skip) and were collected in the same plane: 26 coronal oblique slices perpendicular to the anterior-posterior commissure (AC-PC) line which then underwent a 30° rostral tilt.

The task itself was presented in a block design and lasted 208 seconds per run. Each stimulus remained on the screen for 1.5 sec, with 0.25 sec between stimuli. Participants were instructed to respond as quickly and accurately as possible, and to only answer once per trial even if they knew they made a mistake. Each block consisted of 24 stimuli (42 sec). Each run consisted of 8 blocks of alternating conditions (Interference vs. Control), bookended by 30 sec fixation on a dot in the middle of a blank screen (6 min 36 sec total per run). Data presented here are from Run 1 only.

Behavioral MSIT task responses were recorded by an MRI-safe button

box using the dominant hand. SCR data were collected with a Coulbourn Instruments psychophysiology tower (V15-17) isolated skin conductance coupler (V71-23) connected to a laptop PC. Two SCR electrodes (BioPac Systems, Inc. EL258RT) were filled with isotonic, conductive electrode gel and placed on the hypothenar eminence of the palm of the non-dominant hand, affixed with BioPac adhesive collars (ADD208) and secured lightly with porous medical tape. Analog signals were sampled at 5Hz and digitized by a Coulbourn LabLinc General Purpose Port (V19-16).

FMRI data were analyzed using SPM2. After spatial registration and smoothing (8mm), voxelwise Interference vs. Control (I vs.C) contrasts were computed for each participant. The resulting contrast images were then examined for main effects of diagnosis and exposure, and for a diagnosis x exposure interaction. To obtain whole-brain correlational data, we entered values for the variable of interest (e.g., EXO-LOG score or CAPS-D scores) as a covariate for each participant. BOLD response data from relevant ROIs were extracted using the MarsBaR toolbox (http://marsbar.sourceforge.net). Coordinates for local maxima are reported in Montreal Neurologic Institute (MNI) space. Our a priori threshold for statistical significance is Z=3.09.

F. MSIT fMRI STUDY RESULTS

As a manipulation check, the I vs. C contrast was computed across all participants; this yielded a robust activation in the a priori regions of interest

(ROIs): the dACC, superior parietal cortex, and DLPFC (see Figures 5 & 6). While this is an important and expected finding, the hypotheses centered on whether there were group differences among in the patterns of activation (Hypotheses 5-10).

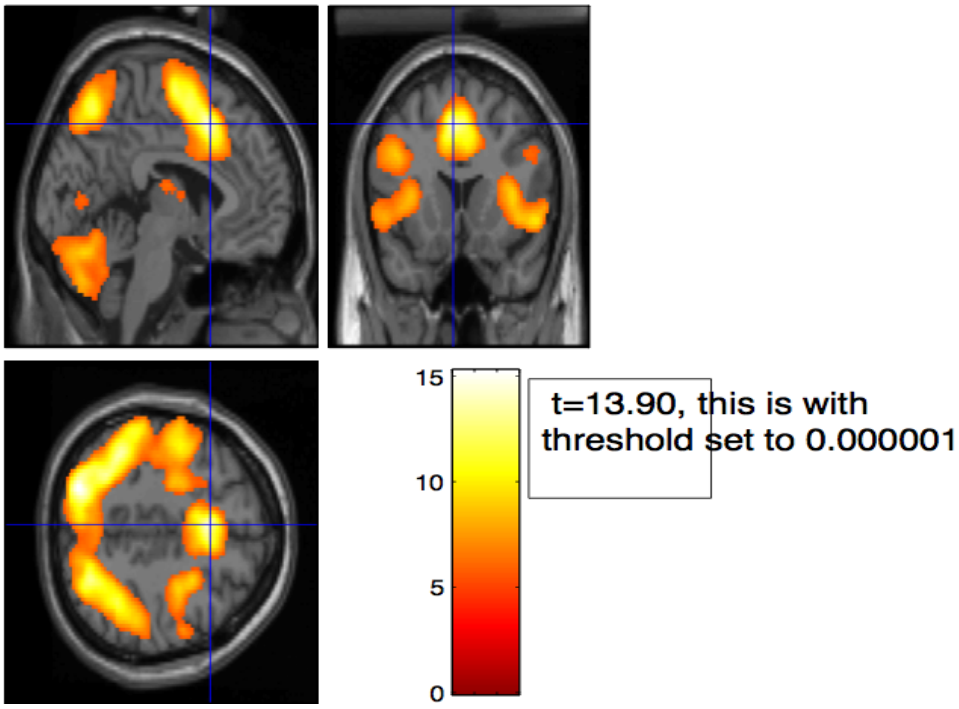


Figure 5. Robust activation of dACC (MNI -4,+16,+46) in the I vs. C contrast of all 54 participants combined, Z > 8.00, BOLD signal is depicted at *p*=.000001 one-tailed. The cluster extended to the dura in the Z plane.

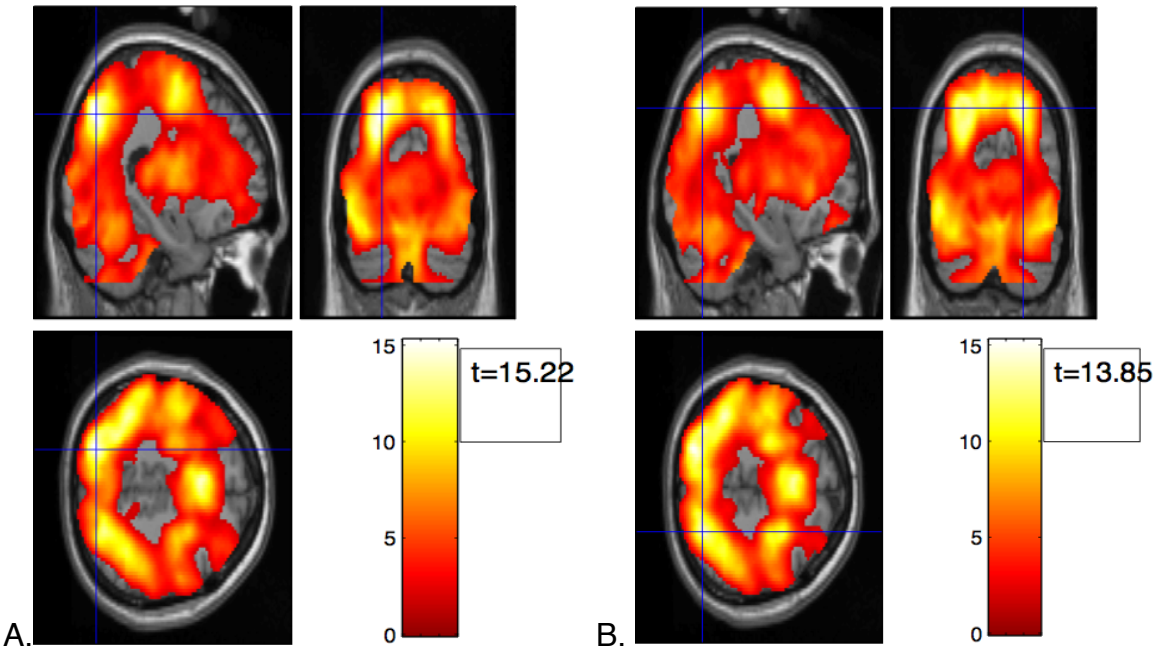


FIGURE 6. BOLD response in bilateral superior parietal cortex, in the I vs. C contrast across all 54 participants. Z > 8.00, BOLD signal is depicted at *p*=.001 one-tailed.

One aim of the MSIT study was a replication of Shin et al. (2011). In that study, there was a main effect of diagnosis on BOLD response in the dACC. Specifically, P+ pairs relative to P- pairs showed greater BOLD response to I vs. C blocks at MNI coordinates +10,+6,+46 and the t-statistic of that BOLD response comparison transformed to a Z score of 3.17 (Shin et al., 2011). In the current MSIT study, we sought to replicate this main effect of diagnosis. In the manner of Shin et al. (2011), we performed a pairs analysis examining I vs. C contrast images combined across twin pairs (n=11 P+ twin pairs and n=16 P- twin pairs or N=54 individuals, see Supplemental Data, Table 5) in which contrasts from combined P+ pairs were contrasted with combined P- pairs. From this independent samples contrast, a dACC ROI emerged at MNI coordinates -

10,+22,+48 with a Z score of 2.46, *p* (uncorrected) = .007, one-tailed (see Figure 7).

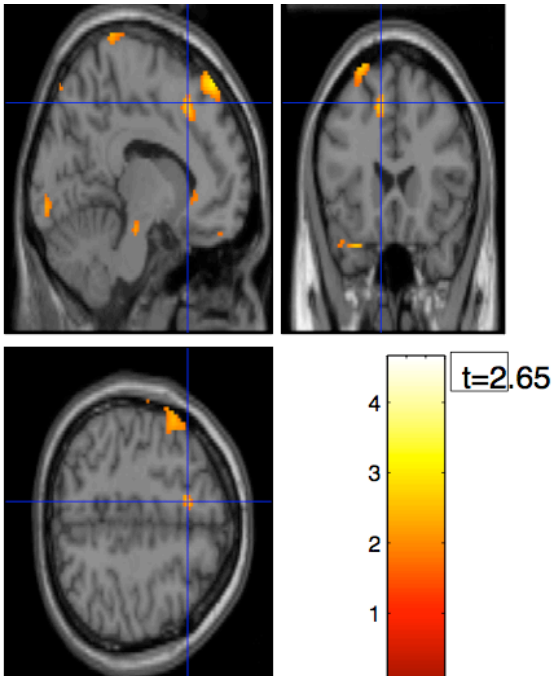


Figure 7. BOLD response in the main effect of diagnosis of the interference vs. control MSIT trials contrast. MNI -10,+22,+48 lies within the dorsal anterior cingulate cortex (dACC). BOLD signal is depicted at *p*=.05 one-tailed.

This ROI activation does not satisfy our group's normal a priori threshold of Z=3.09 (*p* uncorrected = .001, one-tailed). However, given that this is a replication study in a rare population with a small N, and that we found a strong a priori trend in our main region of interest, we investigated further and extracted data from a 4mm sphere surrounding that voxel in the I vs. C contrast of all participants combined. We subjected those individual I vs. C extracted data to a mixed-model ANOVA with combat exposure (Ex, Ux) as the within-subjects factor and PTSD diagnosis (P+, P-) as the between-groups factor, and found a

significant main effect of diagnosis, F(1,25)=5.49, *p*=.014, one-tailed (see Figure 8).

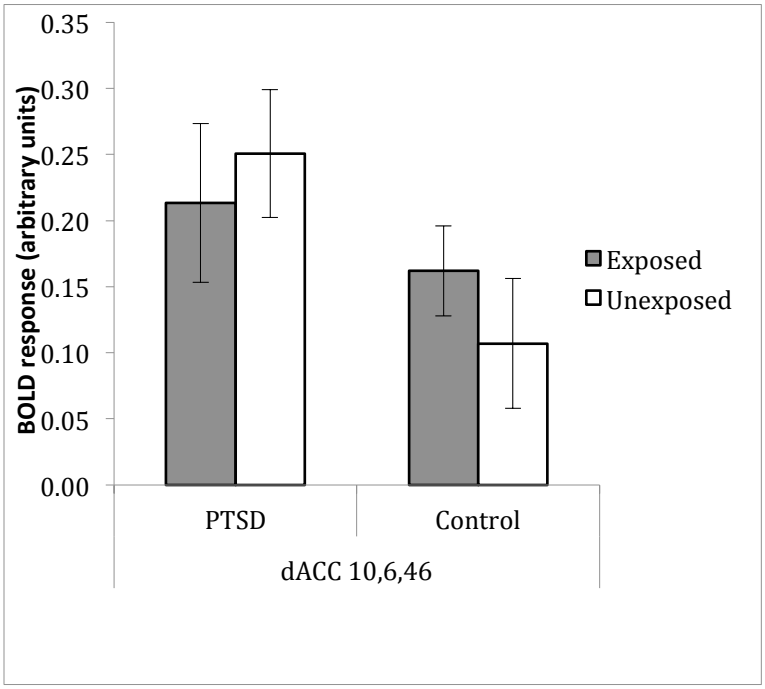


Figure 8. Main effect of diagnosis on individual extracted BOLD responses surrounding peak voxel MNI -10,+22,+48, F(1,25)=5.49, *p*=.014. Neither the main effect of exposure, F(1,25)=0.026, *p*=.87, nor the diagnosis x exposure interaction, F(1,25)=0.74, *p*=.40, were significant.

In order to understand how each condition contributed to the group differences, we extracted data from this dACC ROI for the I vs. Fixation and C vs. Fixation contrasts (see Figure 9).

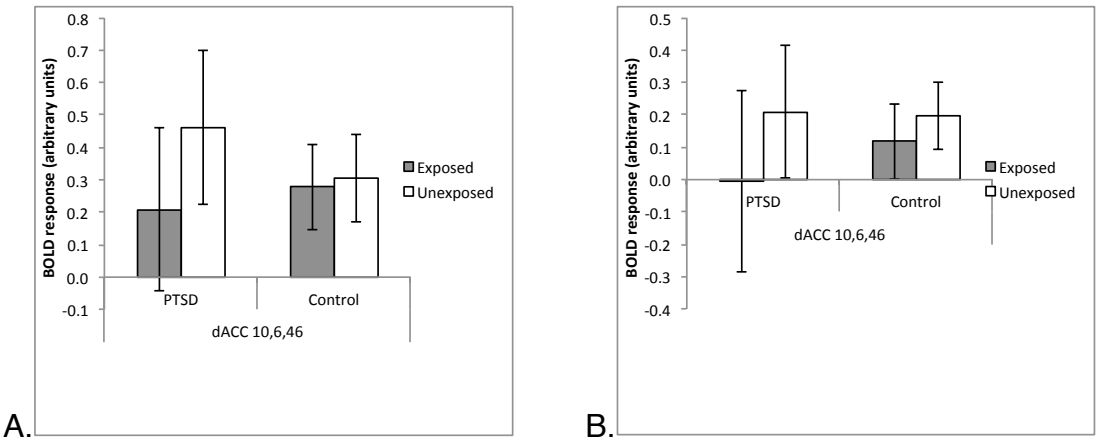


Figure 9. A) I vs. fixation B) C vs. fixation. Data were extracted from the same 4mm sphere surrounding voxel MNI -10,+22,+48 as depicted in Figure 8 above. Each bar in Figure 8 reflects the corresponding bar in Figure 9A minus the corresponding bar in Figure 9B.

The resulting bar graphs were not precisely the pattern one would expect from a true diagnosis main effect, which would be that all participants activate to both I and C relative to fixation, but the activation to I is larger in P+ pairs. Upon examining the extracted data, there was an outlier among the ExP+ participants, with values less than 2 SD below the mean. This pair had been flagged in preprocessing due to excessive movement in the Ex twin (normal threshold is 1° rotation and this individual had up to 8° rotation across both runs) and had been flagged in the first state of analysis due to failure of the Ux twin to activate dACC to the interference condition of the MSIT task. Therefore, we removed that pair and reexamined the diagnosis main effect. The same peak voxel activated in dACC, but with a lower Z score: -10,+22,+48 with a Z score of 2.13, p (uncorrected) = .017 (see Figure 10). Again, despite not meeting the Z=3.09 a

priori threshold, we extracted data.

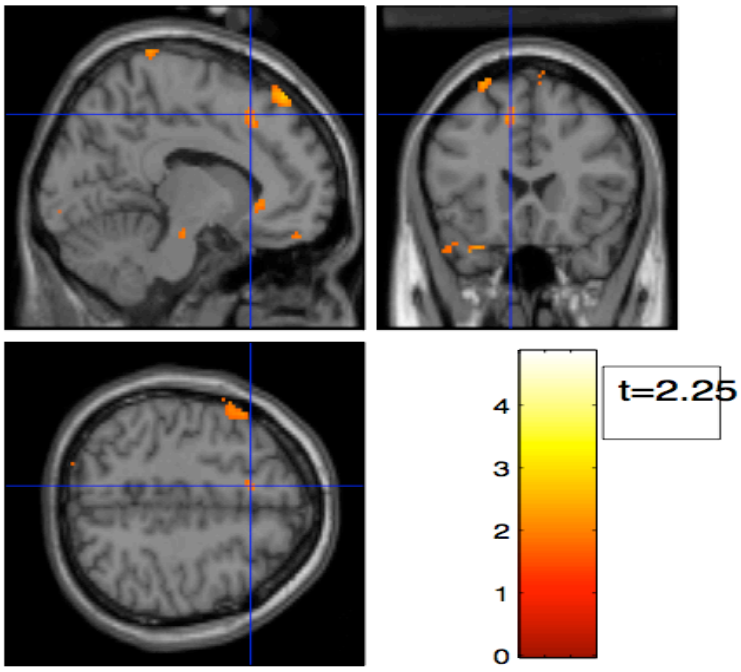


Figure 10. BOLD response in the main effect of diagnosis of the interference vs. control MSIT trials contrast, after the removal of one P+ pair. MNI -10,+22,+48 lies within the dorsal anterior cingulate cortex (dACC). BOLD signal is depicted at *p*=.05 one-tailed.

Extracted data from a 4mm sphere surrounding that voxel in the all-participants-combined I vs. C contrast also produced a significant main effect of diagnosis, $F(1,24)=3.77$, $p=.032$, one-tailed. The main I vs. C bar graph pattern did not look as good as the previous analysis, however the patterns of the I vs. Fix and C vs. Fix bar graphs looked better (see Figure 11).

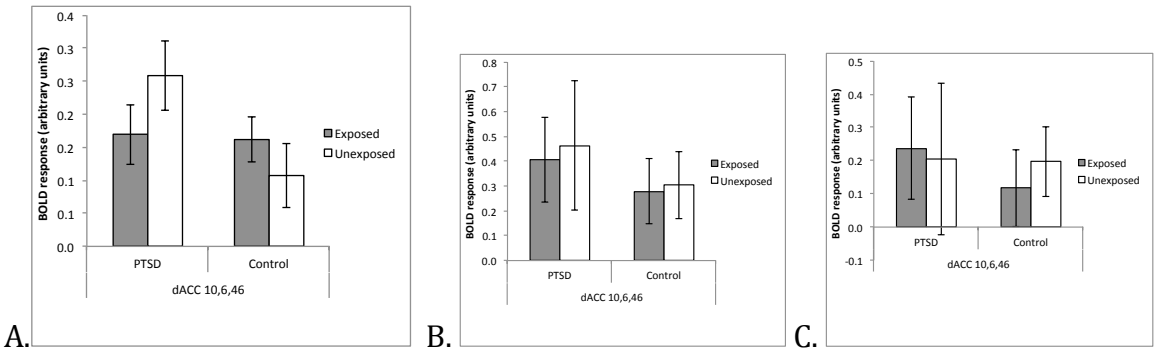


Figure 11. A, B, and C depicting I vs. C, I vs. fixation and C vs. fixation, respectively, after removal of one P+ pair. Data were extracted from the same 4mm sphere surrounding voxel MNI -10,+22,+48 as depicted in Figure 10 above. Each bar in 11A reflects the corresponding bar from 11B minus the corresponding bar from 11C.

Many comparisons also produced patterns of significant effects with slightly imperfect group mean patterns or nice a priori patterns that missed reaching significance. Parietal and DLPFC analyses were not exceptions. The a priori hypothesis (Hypothesis 8) for superior parietal cortex and DLPFC was a main effect of combat exposure; the prediction was that sustained hyperarousal during combat tours would cause Hebbian learning in those structures, interacting with the familial vulnerability factor of lack of dACC-directed cognitive control to give rise to propensity for attentional capture.

In the combined I vs. C contrast map for all participants (Figure 6), strong bilateral activations in both superior parietal cortex and DLPFC emerged. Data extracted directly from those four ROIs were subjected to a mixed-model ANOVA; no effects were significant. Therefore, peak voxel ROIs from each individual's bilateral superior parietal cortex and DLPFC were extracted. (The same technique was examined for dACC and the extracted data were not

significant). In most cases, the peak cluster in bilateral parietal cortex was obvious. In contrast, the frontal cortex generally showed more activation, and so for each participant, the peak voxel closest to ±43,+29,+23 (MNI coordinates) was chosen based on a meta-analysis of DLPFC localization (Cieslik et al., 2013). Subjected to the same mixed-model ANOVA, the individual superior parietal and DLPFC data produced trend-level (.05 < *p*s <.10) significance for the hypothesized exposure main effects, in the right hemisphere only. The bar graphs from extracted right superior parietal cortex and right DLPFC activations are presented in Figures 12 and 13.

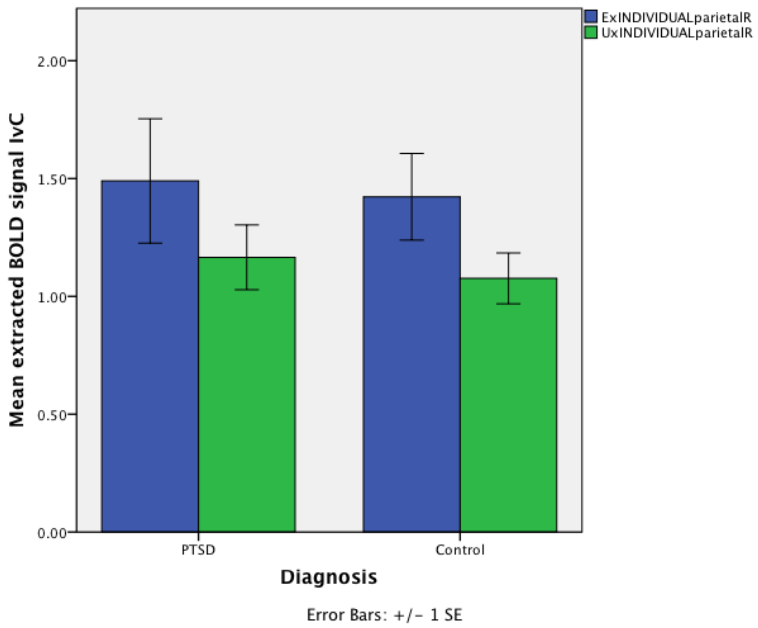


FIGURE 12. Right superior parietal cortex data extracted from each individual participant's I vs. C contrast. Blue=Ex; Green=Ux

Exposure, F(1,24)=2.443, *p*=.066, one-tailed
Diagnosis, F(1,24)=0.343, *p*=.564
Exposure x Diagnosis Interaction, F(1,24)=0.003, *p*=.960

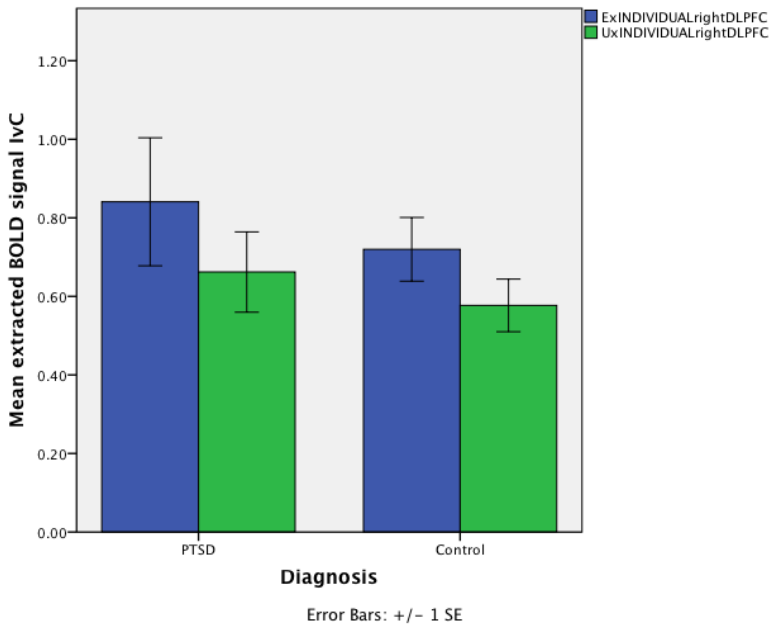


FIGURE 13. Right dorsolateral prefrontal cortex (DLPFC) data extracted from each participant's I vs. C contrast. Blue=Ex; Green=Ux

Exposure, F(1,24)=2.632, *p*=.059, one-tailed
Diagnosis, F(1,24)=0.996, *p*=.329
Exposure x Diagnosis Interaction, F(1,24)=0.033, *p*=.857

The bar graphs of extracted right hemisphere data depict a pattern of results consistent with the hypothesized main effect of exposure; one-tailed *p*-values of .066 and .059 constitute trends towards significance. An EEG study of

Vietnam War nurses from Metzger, et al. (2004) found that PTSD hyperarousal symptoms were associated with increased right-sided parietal cortex activation. However, early papers characterized the top-down, endogenous dorsal attentional network (DAN) as *left*-lateralized and the bottom-up, exogenous ventral attentional network as right-lateralized (Corbetta & Shulman, 2002). More recent studies have characterized both bilateral superior parietal cortex and bilateral DLPFC as comprising the dorsal attention network (Spreng et al., 2013). Indirectly evidencing their coordination within a functional network, the current right hemisphere superior parietal and DLPFC data did show strikingly similar patterns; extracted values from right parietal and right DLPFC were strongly correlated, $r(51)=.691$, $p<.001$, one tailed.

In a separate behavioral analysis performed by M. Kathryn Dahlgren, M.S., Run 1 interference minus control (I-C) response time differences were calculated. Behavioral data were missing for 1 P+ pair and 4 P- pairs, leaving 10 P+ pairs and 12 P- pairs in the correlation analyses. Individual participant's response times were used as covariates in the I vs. C fMRI contrast for all participants combined, to determine whether BOLD activation in any particular brain structure predicted behavior. The a priori brain structures were the dACC, superior parietal cortex and DLPFC. There were trend level correlations for dACC (Figure 14) and right superior parietal cortex (Figure 15), but the DLPFC was not significantly correlated with response time difference scores. Interestingly, there was a strong correlation in right anterior insular cortex (Figure 16) and a strong

negative correlation in posterior cingulate cortex (Figure 17) extending to precuneus. Posterior cingulate cortex is a hub of the resting state default network that tends to anticorrelate with task engagement (Buckner, Andrews-Hanna, & Schacter, 2008; Spreng et al., 2013) and whose functional connectivity negatively predicts vulnerability to PTSD in recently traumatized individuals (Lanius et al., 2010). Precuneus is part of the exogenous, ventral attention network discussed earlier.

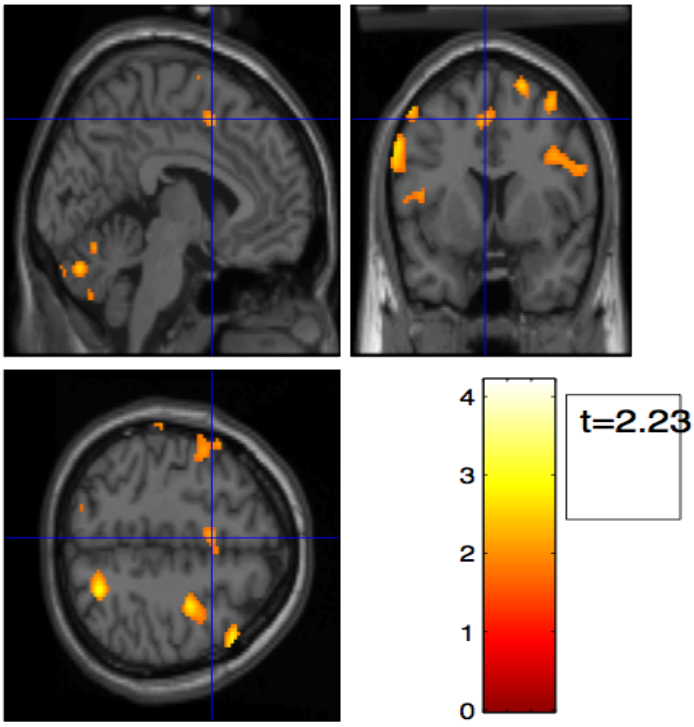


FIGURE 14. MSIT task I-C response time difference scores correlated with I vs. C contrast BOLD response in the dACC, MNI: -4,+8,+50; Z=2.15. Removal of the problematic P+ pair reduced the same peak voxel to Z=2.08.

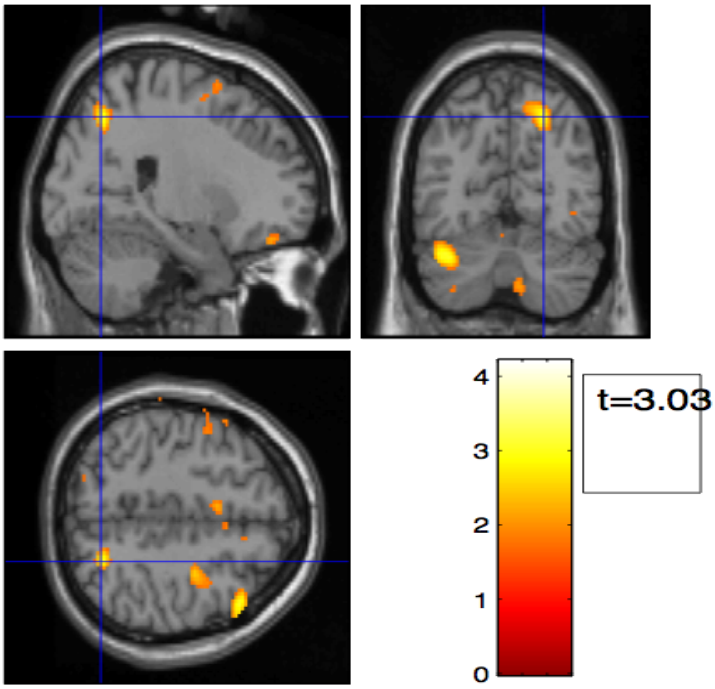


FIGURE 15. MSIT task I-C response time difference scores correlated with I vs. C contrast BOLD response in right superior parietal cortex, MNI: +24,-66,+48; Z=2.86. Removal of the problematic P+ pair increased the same peak voxel to Z=2.93.

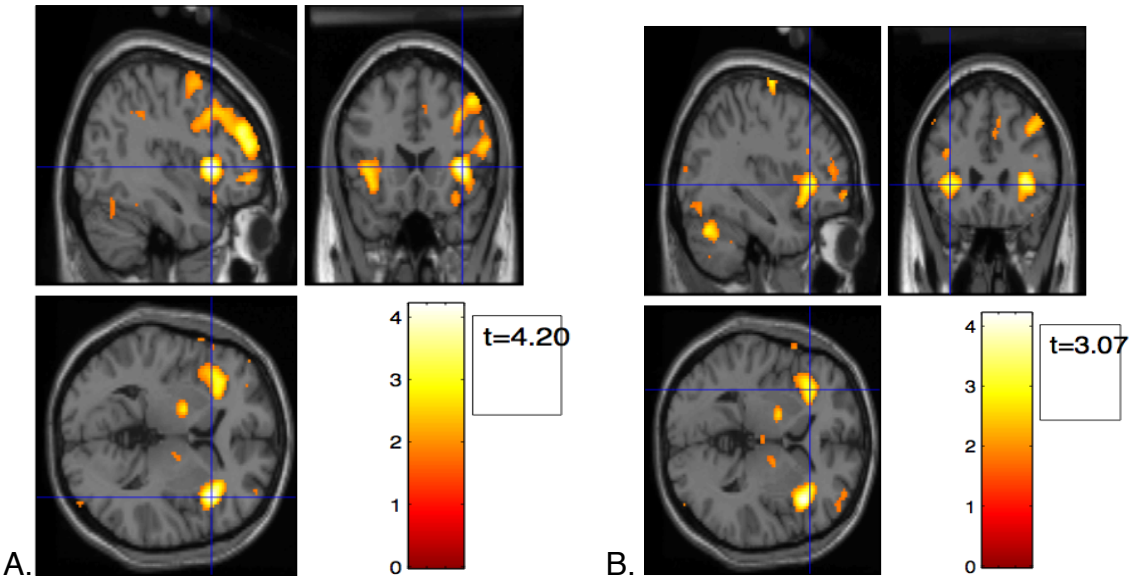


FIGURE 16. MSIT task I-C response time difference scores correlated with I vs. C contrast BOLD response in bilateral insular cortex. Right insula was significant

while left insula was a trend. A) Right insula, MNI: +40,+20,+4; Z=3.81. Removal of the problematic P+ pair decreased the same peak voxel to Z=3.71. B) Left insula MNI: -34,+26,+2; Z=2.90. Removal of the problematic P+ pair increased the same peak voxel to Z=2.92.

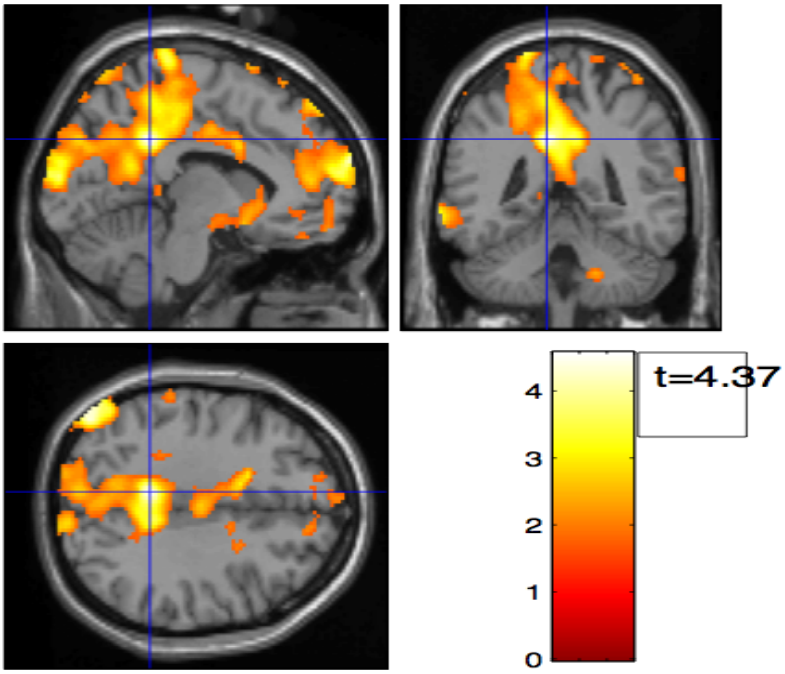


FIGURE 17. MSIT task I-C response time difference scores negatively correlated with I vs. C contrast BOLD response in posterior cingulate cortex, MNI: -8, -44,+34; Z=3.95. Removal of the problematic P+ pair increased the same peak voxel to Z=3.98.

There was also a negative correlation between I-C response time difference scores and I vs. C BOLD response in the medial prefrontal cortex at MNI -4,+62,+16, Z=3.74, but this activation was very close to the edge of the brain.

In terms of symptom expression, the hypotheses of this project relate most strongly to hyperarousal and "problems with concentration" symptoms, which are measured by the hyperarousal subscale (subscale D) of the CAPS. Only trauma-

exposed individuals receive a CAPS score. Therefore, we performed a whole brain analysis correlating each Ex participant's CAPS-D score to their I vs. C fMRI BOLD response. Data from that analysis are presented in Figure 18.

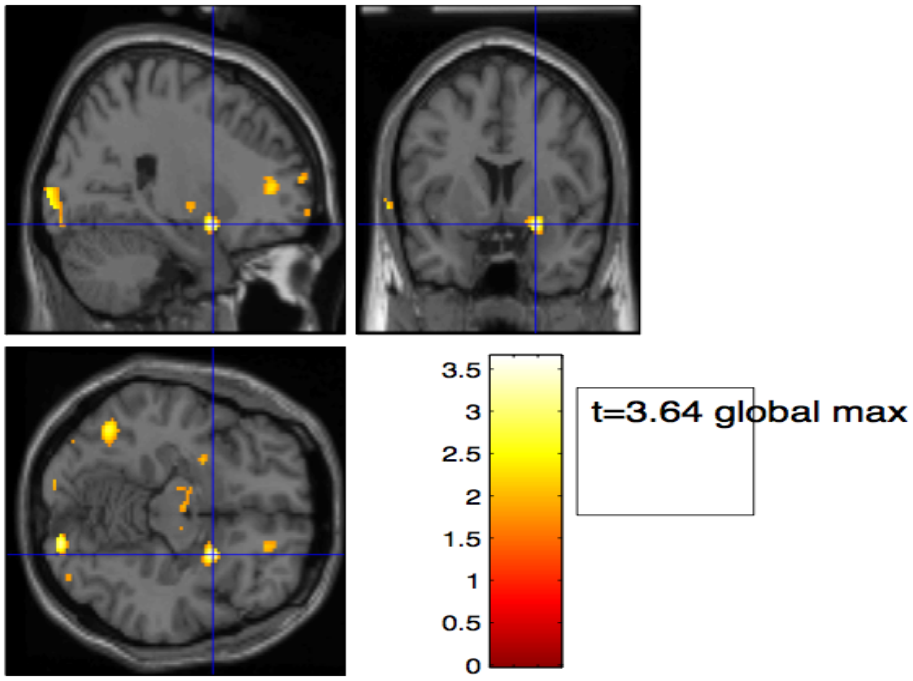


FIGURE 18. Whole-brain positive correlation between CAPS-D scores and the I vs. C contrast BOLD response in the right amygdala of Ex participants. MNI +24,+6,-12, Z=3.23

There was a significant correlation between CAPS-D hyperarousal symptoms and BOLD response to the I vs. C contrast in right amygdala (+24,+6,-12; Z=3.23). There were nonsignificant positive correlations with CAPS-D in left amygdala (-28,0,-8, Z=2.30) as well as dACC (-10,+12,+44, Z=1.98 and +10,+24,+42, Z=2.05). There was a significant negative correlation with CAPS-D in Brodmann 9 of the right hemisphere (+26,+24,+30, Z=3.54).

G. MSIT TASK DISCUSSION & LIMITATIONS

After extracting data from an a priori-but-trend-level ROI in the main effect of diagnosis (I vs. C contrast), we found a significant main effect of diagnosis on those extracted data (p=.014). In principle, this was a replication of Shin et al. (2011) although the failure to meet initial significance in the voxelwise maps and the pattern of extracted data were less than ideal. After removal of a problematic P+ pair, the main effect of diagnosis remained significant (p=.032), and the pattern of extracted better approximated those of Shin et al. (2011). That study also used the MSIT task and the same twin design to find evidence that dACC hyperactivation during this task may represent a biomarker for a familial vulnerability factor for PTSD.

The most likely reason that the initial MSIT task I vs. C contrast did not replicate Shin et al. (2011) is that the study was underpowered due to small N. The small N, in turn, necessitated that we include participant data that might have been excluded in a study with more bountiful recruitment. In addition to the pair that was excluded from the re-analysis of the diagnosis main effect, three other P+ pairs and four P- pairs were flagged during preprocessing for questionable movement in at least one twin. Their inclusion likely contributed to error variance but their exclusion would have substantively reduced statistical power. Future analyses can test the effects of excluding all or some of these pairs. Unfortunately, those pairs that would be excluded for problematic movement were in addition to the four pairs that would be excluded for having failed

behavioral data. In addition, future analyses could take medication use into account as psychiatric drugs can affect BOLD response. Importantly, future analyses should also consider splitting groups by lifetime PTSD instead of current PTSD diagnosis.

Inflated error variance and loss of N was in part due to individual participants' inability to remain motionless in the scanner. In general, blocked designs (of the type we utilized) are more vulnerable to motion artifact than randomized, event-related designs (Aguirre & D'Esposito 2000). The type of gradual movement that occurs across blocks looks jumpy in event-related designs and thus trial presentations covary with movement-based signal changes. Therefore, a reasonable question is whether a randomized design would have been a better choice for the current study (as well as for Shin et al. [2011]). While blocked designs are more vulnerable to signal drift due to motion, they also tend to deliver greater signal power. There may be additional cognitive reasons that MSIT is better in a blocked design than randomized, event-related design. Stins, Van Leeuwen & de Geus (2005) explicitly examined the question of whether the MSIT task shows differential interference effects in a block design relative to a randomized design. Specifically they were interested in two questions: 1) is there a difference in interference effects in blocked vs. randomized presentation of stimuli and 2) what is the relative contribution of flanker interference vs. spatial interference (explained below)?

Regarding the first question, Stins et al. (2005) did find a far greater

interference effect in blocked vs. randomized stimulus presentation. In general, interference tasks using blocked designs tend to have stronger interference effects than when the same task is presented in a randomized event-related design (e.g. Holle, Neely & Heimberg 1997). While one seemingly intuitive interpretation is that blocks of MSIT interference trials are experienced as more difficult than randomized interference trials, a better interpretation may be that blocks of non-interference trials are experienced as easier than randomized non-interference trials. This is because the participant will recognize the onset of a non-interference block and realize that they do not need to think about the number. During a block of the non-interference control condition, participants only have to move their finger according to the spot on the screen that looks different from the other two spots. In randomized or event-related designs, participants must figure out if it is an interference or non-interference presentation on a trial-by-trial basis. All such trials require semantic processing. While the effects are not as large, the randomized design may provide a more pure measure of the effects of interference. To illustrate this point, here is an oversimplified illustration of the comparison being made across conditions.

Block design contrast (Interference *vs.* non-interference Control):

increased interference + semantic processing + motor response

vs.

motor response

Randomized design contrast (Interference vs. non-interference Control):

increased interference + semantic processing + motor response

vs.

semantic processing + motor response

Thus, the answer to the first question posed by Stins et al. (2005) indirectly but strongly supports the use of a blocked design for maximal BOLD-related interference effects.

Regarding the second question from Stins et al. (2005), they were interested in teasing apart effects of flanker interference from spatial interference. For an example, take the interference condition presentation of "221". The correct response is to press the first finger's button. For the same response, a trial in a task with no interference at all would be "1_ _". One source of interference for the 221 MSIT trial is spatial interference - the incongruity between the target ("1") and its location. Without spatial interference (i.e., with only flanker interference), the task would look like "122". There is also flanker interference because the target cue - the numeral 1 - is presented next to potentially-relevant cues, the numerals 2 and 2. Without flanker interference, the task would look like _ _ 1. Perhaps not surprisingly, Stins et al. (2005) found that flanker interference contributed more to total interference than did spatial interference. In this dissertation, the control condition uses the numeral 0 instead of the possible-target numerals 1, 2, or 3. Some published versions of the MSIT even use the letter X (Bush et al., 2003), which seemingly would contribute less

flanker interference, but there is some evidence from our group that using the letter X vs. using distracter numerals does not significantly influence response times (Dahlgren et al., in prep.). The reason that the MSIT is such a robust task is built into its name - there are multiple sources of interference. A fundamental finding of the cognitive load literature is that "the sum is greater than its parts." Interference, like cognitive load, is additive.

Shin et al. (2011) found a diagnosis main effect on BOLD response in the right dACC (MNI coordinates +10,+6,+46), while the current study's dACC effects were left-lateralized. The laterality of this effect may or may not be significant (especially given the 8mm smoothing), but there is a principled anatomical reason to expect right hemisphere effects during fMRI studies of tasks requiring cognitive control. This is despite the fact that, in general, bottom-up detection (and not top-down control) is lateralized to the frontoparietal circuitry of the right hemisphere (Corbetta & Shulman, 2002). The reason is that there is more anatomical variance in the left dACC. At the dorsal boundary of the cingulate gyrus is the cingulate sulcus, which divides Brodmann's area 24 from area 32. In approximately half of all individuals, the cingulate cortex of the left hemisphere only features an additional paracingulate sulcus. This second sulcus increases the spatial variability across individuals in the left hemisphere of the anterior cingulate cortex. The perceived increased spread of activation will reduce the ability to detect BOLD responses in grouped contrasts.

Hypotheses regarding a main effect of diagnosis on superior parietal

cortex and DLPFC were tested using the presence or absence of combat experience as the operationaliztion of "exposed." However, not all Ux participants were totally trauma-naïve and some had civilian trauma. Future analyses may seek to exclude such pairs or control for civilian trauma.

H. INTEGRATION ACROSS TASKS IN THE TWIN COHORT

We performed a whole-brain correlation of BOLD response to the I vs. C contrast with the EXO-LOG score behavioral data of those participants. Figures 19 and 20 show results of interest from that analysis.

Figure 19 depicts a robust correlation of EXO-LOG with left amygdala. The amygdala is a major region of interest in PTSD research, although I would not have expected to see an amygdala relationship with the Posner task. Interestingly, it was the *right* amygdala that correlated with CAPS-D (see Figure 18); CAPS-D in Ex twins also correlated with EXO-LOG scores in Ux twins (see Figure 4).

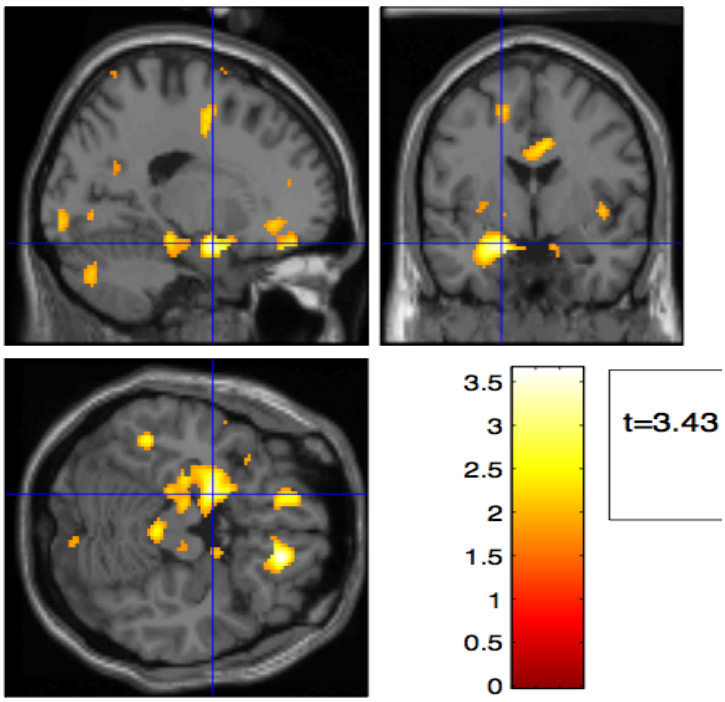


FIGURE 19. Positive correlation between EXO-LOG score and BOLD response to the interference vs. control MSIT trials contrast in the left amygdala, MNI -18,-2,-18 ; Z=3.24.

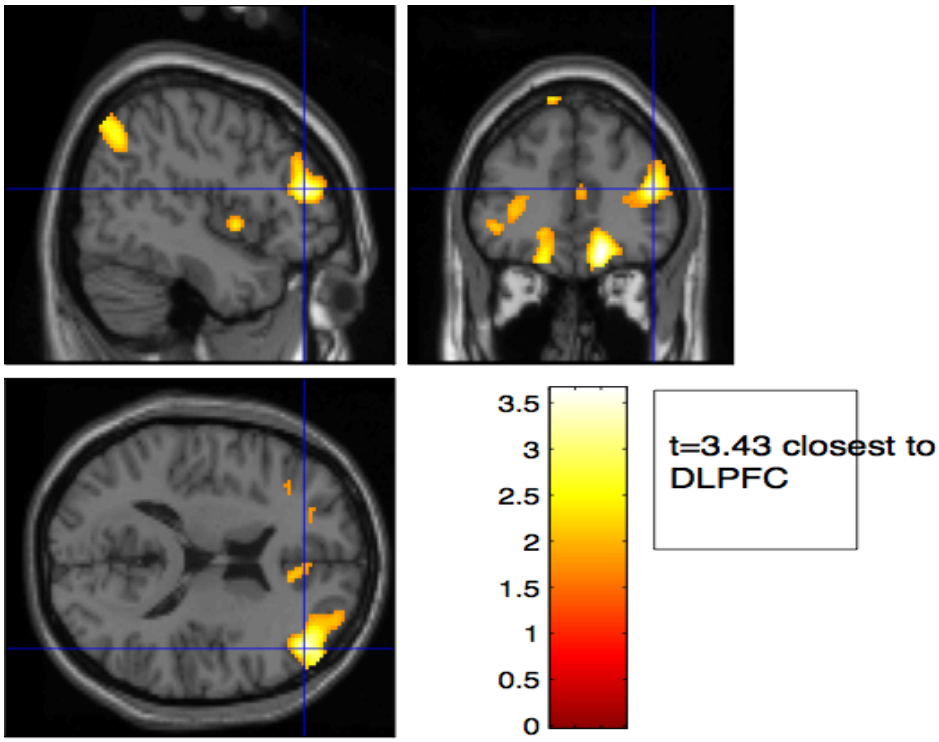


FIGURE 20. Positive correlation between EXO-LOG score and BOLD response to the interference vs. control MSIT trials contrast in the right DLPFC, MNI +46,+40,+16 ; Z=3.24.

There were nonsignificant positive correlations with EXO-LOG in dACC (+8,+6,+28, Z=2.35; +6,-4,+34, Z=2.34; +10,+28,+34, Z=2.16) as well as superior parietal cortex (+50,-66,+44, Z=2.76; +32,-68,+60, Z=2.36; -28,-80,+46, Z=2.31). Unexpectedly, there was a significant positive correlation with EXO-LOG in orbitofrontal cortex (+16,+40,-18, Z=3.42).

Simple correlations using behavioral data were also performed. Response time difference scores in the MSIT task did not correlate with EXO-LOG from the Posner task.

V. DISCUSSION

The primary behavioral finding in these studies was a main effect of diagnosis on the propensity for exogenous attentional capture in the twin cohort, which was correlated with PTSD hyperarousal symptoms. If some individuals have a behavioral pre-trauma vulnerability to PTSD, there must be a neural basis for such a vulnerability. The primary brain finding of these studies was a main effect of diagnosis on hyper-responsiveness in the dACC, a structure implicated in control over attention. Previous studies have found evidence for dACC activation during the Posner task in healthy individuals, especially during incongruent trials (Gómez, Flores, & Digiacomo, 2008). Furthermore, previous studies have also tied neutral stimuli attentional capture to dACC hyperresponsivity and to hypervigilance symptoms in PTSD (Bryant et al., 2005).

Given these findings, the main effect of diagnosis on exogenous attention capture and the main effect of diagnosis on dACC hyperresponsivity will be the primary focus of discussion. An argument will be made that dysfunction in a multi-functional structure such as the dACC can explain several prominent symptoms in PTSD, including exogenous attentional and memory capture, and that both environment and genes could influence vulnerability to PTSD via the dACC.

A. MAIN EFFECT OF DIAGNOSIS

What does a main effect of diagnosis mean? As stated earlier, we cannot rule out the possibility that such a finding reflects the consequences of an experience shared by twins post-trauma. However, it seems much more likely that it reflects a pre-existing vulnerability factor and the discussion will proceed with that assumption. This vulnerability could be related to heritable traits (nature), pre-trauma life experience (nurture), or most probably, the interaction of both. If individuals with PTSD have a hyperactive dACC and if that hyperresponsiveness is actually a pre-trauma vulnerability factor for PTSD, it is reasonable to ask what this hyperresponsiveness represents and why it would lead to functional problems. Assuming that dACC hyperresponsiveness is reflected in some aspect of cognition, it could represent:

-**Inefficient signaling**: more effort to accomplish the same task
-**Coping with symptoms**: ongoing interference resolution & effortful attention, independent of current task
-**Primed signaling**: anticipatory depolarization for task- or fear expression-readiness that ends up hurting signal-to-noise

It is feasible that the above reasons for hyperresponsivity in dACC could relate to different tasks and paradigms, and that more than one of these processes could occur at any given time. Furthermore, BOLD response differences could reflect

GABAergic or glutamatergic processes. But any of the above would broadly diminish each aspect of dACC functionality. Therefore, regardless of what the hyperresponsive BOLD response represents, understanding normal dACC function is likely to be important in understanding how dACC dysfunction precipitates or maintains PTSD symptoms. The following text begins with a discussion of general theories of dACC function, and then relates these considerations to PTSD.

B. DACC FUNCTION & PTSD: CONTROL & FEAR

Neuroscience has long been preoccupied with attempts to tie structure to function. With the emergence of the holist/localist debate (ironically coinciding with the rise of phrenology), theories of "modularity" began to question the assumption that the brain is a homogenous organ, arguing that it is rather composed of different structures with interacting but different functions (Finger, 1994). When thinking about the function of specific structures, there is a spectrum of possible functional specificity, with its most extreme expressions varying from early theories describing brain as a uniform mass of functionally indistinguishable tissue (extreme holist position) to the "cellular engram" - the idea that a single memory is contained in a single cell (extreme localist position). The truth is likely between these two extremes, but modern neuroscience has come down firmly on the "localist" half of the debate, with relatively specific functions assigned to brain structures and circuits. Evidence for specific functions

for the dACC and a review of some of the ongoing debate are discussed below.

1. Cognitive dACC Function Theories & Integration

As discussed earlier, the most influential model of PTSD is the fear conditioning model (e.g., Orr et al., 2000; Pitman & Orr, 1986; VanElzakker et al., 2014). PTSD is also associated with increased amygdala activation during extinction learning, relative to trauma-exposed individuals without PTSD (Milad et al., 2009). The dACC is also a crucial node in the expression of conditioned fear and has been shown to be hyperresponsive in individuals with PTSD during fear conditioning acquisition and fear extinction recall (Milad et al., 2009; Rougemont-Bücking et al., 2011), which are considered to be proxies for PTSD acquisition and maintenance. Importantly, dACC hyperresponsivity does not only occur during fear conditioning and extinction paradigms, but also during paradigms that include trauma-related, emotionally valenced, and emotionally neutral stimuli - essentially, all kinds of cognitive and emotional experiences (reviewed in VanElzakker, Staples, & Shin, in press). Resting metabolic rate for glucose is even elevated in the dACC of individuals with PTSD (and their trauma-unexposed identical twins; Shin et al., 2009), suggesting that dACC dysfunction is a general trait. The dACC is clearly involved in a great many tasks, subjective experiences, and forms of cognition; consequently, it may be difficult or impossible to reduce its function to a single mechanism. Nevertheless, a literature dedicated to parsing normal dACC function in healthy individuals has made significant progress in clarifying the type of processes that may especially rely on that structure, and in

understanding the behavioral and psychiatric effects that may result from dACC dysfunction.

One thing that is clear is that the dACC has access to diverse information across cognitive and emotional realms. Broadly, three realms of normal healthy dACC involvement include processing related to cognitive control, emotion, and pain. Relatively early in the era of functional neuroimaging, evidence pointed to functional segregation within the anterior cingulate cortex. Such studies evidenced a cognitive-emotional split in cingulate function, such that cognitive information was processed in the more dorsal cingulate (dACC) while emotional information was processed in the ventral/rostral cingulate (rACC). An early and influential paper reviewed evidence for such functional segregation within the anterior cingulate cortex, and found that evidence to be strong (Bush, Luu, & Posner, 2000).

With the accumulation of new data, that relatively simple model has lost favor as more and more findings have violated simple cognitive/emotional segregation. As opposed to strict anatomically segregated function, some theorists propose a functional/anatomical continuum of emotional-cognitive processes from rostral to dorsal ACC (Mohanty et al., 2007). Still newer theories have emphasized the role of integration in dACC function: integration of cognitive and emotional information as well as information about bodily state (such as pain; Shackman et al., 2011). The nature of that integration is still being debated. While it is now clear that there is not a functional segregation between relatively

large gross subregions of the cingulate cortex, this does not mean that there is no functional segregation within that structure. It is likely that specific neurons are part of separable circuits involving attention, cognition, emotion, pain, and the relative integration among those faculties. For example, Davis, Hutchison, Lozano, Tasker, & Dostrovsky (2000) conducted direct single-neuron microelectrode recordings in nine individuals undergoing cingulotomy for intractable MDD or OCD. These patients participated in several attention-demanding cognitive tasks. Davis et al. (2000) found that 19% (7) of the 36 total neurons tested responded in some fashion - either with excitation or inhibition - to at least one of the tasks. None of those neurons responded to pain (pin pricks or hot or cold applied to the skin). However, a previous study from the same group did find pain-responsive neurons in the cingulate cortex (Hutchison, Davis, Lozano, Tasker, & Dostrovsky, 1999). This suggests that, while BOLD response may not have the spatial resolution to dissociate specific functional circuits, it does not follow that such circuits do not exist.

Despite comprising separable functional circuits, one possible function of the dACC is that it serves to integrate information across these domains (cognition, emotion, and pain), as such integration relates to an ongoing goal or situation (Shackman et al., 2011). The dACC's role in integration may include targeted integration across domains, for example, assigning the appropriate emotional response to pain. For example, it cannot be the case that humans simply avoid anything that causes them pain; else, they would never have a

second child, go jogging, or complete doctoral theses. There must be a way to "overcome" the purely negative experience of pain with the recognition that such pain actually leads to long-term reward. The dACC may be an important structure for evaluating the subjective emotional and factual meaning of the negative experience of pain, including what predicts it and whether it can be controlled.

Involvement in the processing of errors or, relatedly, the processing of expectation violations is another such cross-domain candidate for dACC function. An example of this is "negative surprise" in which an expected outcome fails to materialize (Egner, 2011). Error detection clearly activates the dACC (Botvinick, Cohen, & Carter, 2004; Bush et al., 2002), but there are several ways such a signal could be interpreted. At the risk of anthropomorphizing a brain structure, one interpretation is that the dACC itself actually detects the error. Such a function does not require anthropomorphizing, however, if the morphology of the structure facilitates the function. An example of this is the way that the structure and circuitry of the hippocampus facilitates the detection of contextual novelty by serving as a "comparator" between already-existing episodic memories and ongoing experience (VanElzakker, Fevurly, Breindel, & Spencer, 2008). However, another is that the dACC is evaluating the nature of the error, specifically whether or not the individual or organism has *control* over the error. Such a determination is important for learning; one must first know whether an error was even avoidable (or if a negative experience is controllable) before one can take corrective action.

Another related model could be that the function of such integration is to inform the necessity of cognitive control. While terms like "cognitive control" and "executive function" are debated and somewhat nebulous, I will use cognitive control as a specific form of executive function. Thus, executive function is defined as "the set of abilities required to effortfully guide behavior toward a goal, especially in nonroutine situations" (Banich, 2009, p. 89) and cognitive control is the ability to inhibit a prepotent response that may normally be appropriate but is not appropriate in that specific non-routine situation. Cognitive control is a form of endogenous, top-down control, especially when such control occurs during distraction of some sort. This is the endogenous top-down control discussed in the introduction as it related to the AtM hypothesis (the prepotent response in the MSIT task would be to respond to spatial location and not numeral value; the prepotent response in the Posner task would be to pay attention to distractor cues).

Yet another non-mutually-exclusive possibility is that, rather than serving one function that involves integrating different domains, the dACC performs a similar function across multiple domains. Shenhav, Botvinick & Cohen (2013) reviewed the cognitive control literature relating to human dACC function, and proposed an "integrative theory" of dACC function called "expected value of control" (EVC). According to this theory, the function of the dACC is related to calculating the amount of cognitive control needed for a given outcome and, relatedly, whether exertion of that control is worth the expected outcome. The

authors summarize this function by saying, "EVC represents the net value associated with allocating control to a given task" (Shenhav et al., 2013, p. 217). So, in their conceptualization, dACC activation during the MSIT could represent three related but separable processes: motivation, specification, and regulation. However, the cognitive control exerted during MSIT does not seem to involve much actual "value." No ongoing feedback, end-of-task performance-based reward, or external error signal is given to participants. Interestingly, patients undergoing cingulotomy performed the MSIT during direct neuronal recording of dACC (Sheth et al., 2012), and the responses coincided not with task onset but with ongoing updating of expected task demands.

In general, the EVC theory is rather "reward-centric" and as such does not readily explain dACC (dys)function in PTSD, which centers around memory and fear and not around prediction and reward. The Shenhav, Botvinick & Cohen (2013) review article (subtitle: "An Integrative Theory of Anterior Cingulate Cortex Function") contained neither the words "stress" nor "fear." Given the fundamental role of dACC in the expression of learned fear, any integrative theory of dACC function (the creation of which is not the goal of this paper) must take that role into account. The EVC theory of dACC function seems rather related to "The Adaptive Control Hypothesis" of (Shackman et al., 2011), in which the dACC detects the need for control and exerts it when such control would be adaptive. Shackman et al. (2011) did briefly mention the role of dACC in stressor controllability, a topic that will be expanded upon below. The Adaptive Control

Hypothesis further emphasizes the concept of integration as the function of dACC, a function that relates to its role in fear conditioning.

Pavlovian fear conditioning provides a model that explains fear acquisition in PTSD, and the failure of fear extinction is thought to model the persistence of some symptoms. Several, but not all, previous studies have shown increased acquisition of conditioned fear in PTSD and most studies have shown deficits in fear extinction learning and/or recall (reviewed in VanElzakker et al., 2014). The dACC plays an important role in the expression of this learned fear, and in the initial learning of the CS-US (conditioned stimulus-unconditioned stimulus) association (Milad et al., 2007). This function allows the dACC to operate as a control switch, assigning appropriate control to other areas of the brain including the amygdala and motor systems for fear, fight, or flight (Gabbott, Warner, Jays, Salway, & Busby, 2005). This seems to be a more inclusive definition of dACC function: the dACC integrates internal subjective experience with the most relevant external information in a way that facilitates development of the most appropriate response or inhibition of response. Part of that function is to determine whether an alleviating response to a stressor is even possible, that is, if the stress is controllable. If dACC functionality is diminished by non-adaptive hypeactivity and hyperresponsivity, its capacity to detect controllability will be diminished and all stressors are more likely to be interpreted as uncontrollable. An example of cross-symptom effects from dACC dysfunction is presented here.

2. dACC Cross-Domain Integration & PTSD Symptoms

The dACC is involved in the integration of faculties such as cognitive control, learned fear, pain, reward and error monitoring, and interference resolution. Regardless of the nature of such integration in dACC, domain-crossing functionality within this structure may help to explain some of the diversity in PTSD symptoms because dACC dysfunction will have broad effects. For example, there is a high rate of comorbidity between PTSD and chronic pain (Asmundson & Katz, 2009). An estimated 15-35% of chronic pain patients have PTSD (National Center for PTSD, n.d.). While some of this may be explained by the covariance of traumatic injury leading to both chronic pain and PTSD, there is also shared involvement of the dACC in both conditions.

For example, skin conductance responses (SCR) are a commonly used measure of sympathetic nervous system activity and are frequently used psychophysiological measures in PTSD studies (reviewed in Pitman et al., 2012; VanElzakker et al., 2014). Milad et al. (2007) showed that, in healthy individuals, dACC BOLD response during fear conditioning is positively correlated with differential SCR. Individuals with PTSD show greater SCR startle responses (Orr et al., 2003; Orr, Metzger, & Pitman, 2002; Pitman et al., 2006). Many studies have also shown that the dACC and amygdala are hyperrespponsive in PTSD (VanElzakker et al., 2014; VanElzakker et al., in press). In otherwise healthy individuals, the experience of pain increases those PTSD-related phenomena: Pain amplifies the SCR startle response in healthy individuals (Crombez, Baeyens, Vansteenwegen, & Eelen, 1997); those individuals with greater SCR to

pain also had increased BOLD responses in the dACC and amygdala (Dubé et al., 2009), the structures that are hyperresponsive in PTSD. Directly connecting the dACC to increased pain in PTSD, (Strigo et al., 2010) found increased dACC BOLD response to experimental pain in women with intimate partner violence-related PTSD relative to nontraumatized control women.

It is likely that other such cross-domain consequences result from pre-existing dACC dysfunction. In a large, complex brain structure involved in a multitude of diverse processes, two pivotal functions for PTSD vulnerability and maintenance may involve stressor controllability and the expression of conditioned fear. From the animal literature emerges specific dACC-related brain circuits that may underlie a vulnerability that would make an individual more likely to decompensate into PTSD after experiencing a traumatic stressor. In the sections that follow, I will argue that a main effect of diagnosis on dACC function may similarly represent a familial vulnerability factor that involves the interaction between cognition and emotion, including both a propensity to interpret stress as uncontrollable and an inability to learn and recall that a fearcue no longer predicts danger. An exploration of the relationship between dACC and the psychological functions of stressor controllability and the expression of learned fear follows here.

3. Stressor Controllability and the dACC

The dACC is an important hub through which genetics and environment can exert influence on a key underlying mechanism for PTSD symptoms: fear

conditioning and extinction failure (VanElzakker et al., 2014). The current study, as well as previous studies (e.g., Shin et al., 2011) provide evidence that dACC dysfunction reflects a familial vulnerability factor for PTSD. A familial vulnerability factor could comprise shared environmental experience, shared genetics, or both. First, we will argue that environmental experiences can have an effect on fear conditioning and extinction. One such environmental life experience is trauma itself - the prior experience of traumatic stress is a significant vulnerability factor for PTSD (reviewed in Keane, Marshall, & Taft, 2006; Stein, Jang, Taylor, Vernon, & Livesley, 2002). A greater "trauma load" may be contributed by prior stress depending on the characteristics of that prior stress, including severity, type (e.g., sexual), age of trauma, and duration of trauma. A related and potentially important factor may be the extent to which that stress was perceived as controllable. As will be reviewed below, the behavioral and biological response that an organism mounts to stress differs widely depending on whether or not the organism had any control over that stress (Maier & Watkins, 1998). Interestingly, the propensity to respond to stress as though it were uncontrollable (whether or not it actually is) may itself be a familial vulnerability factor that is modulated by dACC function. I propose that the distinction between controllable and uncontrollable (sometimes called escapable and inescapable) stress may be important for understanding dACC function in PTSD. A review of the stressor controllability literature, as it relates to the dACC, follows here.

The rodent brain homologue to the human dACC is the *prelimbic cortex*

(the rodent homologue to human vmPFC is the infralimbic cortex; reviewed in (Milad & Quirk, 2012; VanElzakker et al., 2014). Extensive research has delineated the role of the prelimbic cortex in both the expression of conditioned fear (reviewed in Sotres-Bayon & Quirk, 2010) and in the experience of stressor controllability and its consequences (reviewed in Maier, 2015). A brief review of the rodent stressor control literature follows here; a similar role for dACC in humans is likely and directly relates to bottom-up attentional capture (explained later).

Formerly known as "learned helplessness," the stressor controllability literature has demonstrated the importance of subjective psychological experience during stress. A simple, but compelling, experimental manipulation illuminates this difference (reviewed in Maier, 2015). For example, two rats are placed in separate but adjoining cages, each with its own wheel in the front of the cage; the cages share a metal grid floor. When small electric shocks start pulsing through the floor, spinning the wheel in one of the rat's cages, but not the wheel in the other cage, can turn off the shock. Because the floor is shared, it turns off the shocks for both rats (i.e., both rats always experience the same number and intensity of shocks). Thus, the only experiential difference between the two rats is that one has behavioral control over the shocks and the other does not. This seemingly-minor and totally subjective difference has profound and long-lasting effects, including effects on cognition, immunology, behavior, and neurobiology (reviewed in Maier & Watkins, 1998, 2005). Many of those effects overlap with

human PTSD symptoms. For uncontrollable stress to exert such effects controllability must first be detected and then it must cause functional changes in relevant neurocircuitry. The rodent dACC analogue, the prelimbic cortex, is responsible for both of these processes.

a. Prelimbic cortex detects stressor controllability

The human psychological literature has produced theories for dACC function that focuses on "Expected Value of Control" and "The Adaptive Control Hypothesis" reviewed above. The animal stress and learning literature has expounded a theory of prelimbic cortex function that may also be worth integrating into theories of dACC function.

Maier (2015) had made the point that the detection of stressor controllability is essentially a conditional probability problem of the type that drives instrumental learning. Instrumental learning, in turn, is frequently divided into "act/outcome" and "habit" systems; the former allows for flexible, reward-sensitive learning about the contingency between response and reward, whereas the latter is only concerned with the temporal paring of stimulus and reward (or punishment). The important relationship between the instrumental learning literature and the stressor controllability literature is that the same corticostriatal circuitry is involved in both processes. Crucially, the animal literature evidences that stressor controllability is *detected* in prelimbic cortex circuitry. Therefore, I hypothesize that among the PTSD-related consequences of pre-existing dACC dysfunction is the decreased ability to recognize that one has any control over

ongoing stress. This provides a potential brain basis for why "external locus of control" is a cognitive vulnerability for developing PTSD (Keane et al., 2006). Individuals with dACC dysfunction may simply be less able to detect that their actions can effect change during stress. In other words, there is a failure to engage the contingency-sensitive "act/outcome" system.

Extensive work in rats in the instrumental learning literature has shown the "act/outcome" system to be driven by prelimbic cortex to dorsomedial striatum circuitry, while the "habit" system is driven by sensorimotor to dorsolateral striatum circuitry (Balleine & O'Doherty, 2010). Inactivation (or lesion) of the prelimbic cortex prevents the flexible learning of the act/outcome system, while the more linear habit system does not involve prefrontal cortex (Balleine & O'Doherty, 2010; Maier, 2015). Previous research has also demonstrated that the detection of stressor controllability activates and requires prelimbic cortex (Amat et al., 2005). Without a properly functioning prelimbic cortex, even controllable stress may be interpreted as uncontrollable. Correspondingly, more recent research by Amat et al. (2014) has shown that controllable stress, but not uncontrollable stress, selectively induces Fos protein expression in the dorsomedial but not dorsolateral striatum of rats. Fos is the protein product of *c-fos,* an immediate early gene whose transcription and translation reflects recent cellular activity (i.e., it is a signal that neurons have been firing; VanElzakker et al., 2008; VanElzakker et al., 2011). This is evidence that detection of control engages the act/outcome system but not the habit system. Furthermore, Amat et

al. (2014) examined the effects of dorsomedial or dorsolateral striatum inactivation with microinjections of the NMDA antagonist AP5 before controllable or yoked uncontrollable stress. Like inactivation of prelimbic cortex (e.g., Baratta et al. 2007; Amat et al., 2005), inactivation of dorsomedial striatum by AP5 blocked the "immunization" effects of stressor controllability (discussed below). This is evidence that the prelimbic-dorsomedial striatum circuitry of the act/outcome system is involved in the detection of stressor controllability. Assuming that the same basic circuitry is preserved across species, one would hypothesize that dysfunction in the dACC of humans would render an individual less likely to detect the presence of controllability during a stressor. This could be part of what explains individual differences in PTSD vulnerability.

Previous research has demonstrated that individual differences in rats in susceptibility to uncontrollable stress may involve engagement of the habit system and failure to engage the act/outcome system (VanElzakker et al., 2011). Exposing caged rats to a cat (a potential predator) is a type of biologically relevant stressor that can interfere with normal radial arm water maze performance (a hippocampal-dependent spatial memory task). Interestingly, some rats tend to be more affected than others. VanElzakker et al. (2011) sought to understand what functional neurocircuitry differences might lie at the root of those behavioral differences in the hopes of informing individual differences in vulnerability to PTSD.

Before radial arm water maze training, rats were exposed to a cat by

placing a small amount of cat food on top of the rat's cage. After maze training and testing, rats were split into "Good" and "Bad" performers, and their brains were extracted for analysis. A cellular assay called in-situ hybridization was used to detect *c-fos* immediate early gene mRNA. "Good" performing rats had more *c-fos* mRNA in the dorsolateral striatum, evidencing increased activity in that structure during radial arm water maze performance. This dorsolateral striatum engagement was hypothesized to reflect a "habit" response, with rats using external room cues as opposed to a spatial learning strategy. Differences in the immediate response to cat stress were not detectable, but a "habit" response would reflect those behavioral differences in water maze performance expected of a rat that had experienced the stress as uncontrollable. While the "habit" strategy was associated with good performance in this particular task, it likely reflected disengagement of the hippocampus, the structure that would normally subserve spatial learning. Unstressed rats had more *c-fos* in dorsal hippocampus than rats exposed to cat stress. Reduced hippocampal function is a likely mechanism for PTSD in humans (Zoladz & Diamond, 2013) and thus, other brain structures "taking over" for the hippocampus may reflect individual differences in vulnerability to PTSD-congruent responses to stress. In this case, the habit system provided an alternate learning strategy, perhaps because the cat stress was interpreted as uncontrollable by that group of rats.

After *detection* of controllability or lack thereof, the prelimbic cortex is also responsible for conferring the differential behavioral and biological *effects* of

controllable vs. uncontrollable stress.

b. Prelimbic cortex confers the behavioral effects of stressor controllability

From the detection or failure to detect stressor controllability follows the behavioral consequences of uncontrollable stress, in circuitry that also centers on the prelimbic cortex (dACC). Most relevant to PTSD, the effects of uncontrollable stress include exaggerated fear conditioning and impaired fear extinction learning, as well as exaggerated attention to external stimuli (exogenous or bottom-up attentional capture). Furthermore, it is not simply the case that the experience of control attenuates these negative effects. Rather, an experience with controllable stress causes "immunization" (Maier & Seligman, 1976; Williams & Maier, 1977), meaning that the experience of control can actually block the negative effects of future uncontrollable stress (Christianson et al., 2012; Maier & Watkins, 2010). The "immunization" phenomenon may be a mechanism behind the fact that low-level (assumedly controllable) stress during childhood is a resilience factor, while child abuse (an uncontrollable stressor) is a vulnerability factor for PTSD. Those childhood experiences interact with 5-HT-related genes to predict health or psychopathology such as PTSD (Stein, Campbell-Sills, & Gelernter, 2009; Stein, Schork, & Gelernter, 2008).

Rat research has demonstrated that those lasting immunization effects due to the experience of behavioral control over stress are crucially reliant upon the prelimbic cortex. Prelimbic interaction with the serotonin (5-HT) system is

particularly relevant. What makes prelimbic/dACC involvement in stressor controllability so relevant to PTSD is the profound effects stressor controllability has on exogenous attentional capture, as well as on fear conditioning and extinction.

While it would be difficult to compare cognitive control in rodents and humans, Lee & Maier (1998) provided convincing evidence that uncontrollable stress facilitates exogenous attentional capture in rats, at the expense of goal-driven endogenous attention. They used task-irrelevant distractor stimuli (black and white cards) during a simple left-right spatial discrimination task (similar to a Y-maze, but in opaque lukewarm water with an escape platform in the goal arm) that followed escapable (i.e., controllable), yoked inescapable (uncontrollable), or no shock restrained controls. In a series of three experiments, they demonstrated that, following inescapable shocks, rats paid more attention to these distractor cues whether or not they were helpful; in other words, the internal top-down goal of left-right discrimination became subservient to bottom-up external stimuli. By experiment number:

1) When the location of distractor cues (e.g., white and black were pseudorandomly moved) was made systematically irrelevant to the location of the correct response (e.g., left), rats that had experienced uncontrollable stress were slower to learn than the other groups. There were a greater number of mean trials to criterion (8 correct responses within 10 trials) for the yoked inescapable shock group, relative to the escapable shock and no shock groups.

2) When both possible responses (left & right) were marked with the same distractor cue (e.g., both white or both black), there was not a difference in learning among the groups.

3) When the location of one distractor cue (e.g., white) systematically predicted the location of the correct response (e.g., left or right), the uncontrollably-stressed rats were faster to learn than the other groups.

These experiments demonstrate that the uncontrollable stress group was more influenced by exteroceptive cues, that is, they were more prone to exogenous attentional capture. The three experiments are somewhat analogous to the Posner task's incongruent, neutral, and congruent trials, respectively. EXO-LOG would reflect an experiment 3 minus experiment 1 difference score. According to the authors, "(these experiments) point to attentional processes as one focus of the cognitive changes produced by inescapable shock and suggest that exposure to inescapable shock biases attention away from 'internal' response-related cues toward 'external' cues" (Lee & Maier 1988, p.302). In the vernacular of human attention literature, the changes produced by uncontrollable stress (or brain dysfunction that mimics those changes) bias attention away from endogenous (top-down) control to exogenous (bottom-up) attentional capture. While this would be difficult to test empirically in animal models, given the AtM hypothesis discussed in the introduction, one would infer that these effects on exogenous attentional capture also generalize to attentional capture by salient memories. The animal literature also evidences that, in addition to its effects on

attention capture, the consequences of uncontrollable stress also mimic another PTSD-related phenomenon: increased conditioned fear and decreased fear extinction.

Early work on the effects of stress on fear learning from Rau, DeCola & Fanselow (2005) found that prior stress (tailshock) in one environment facilitated subsequent fear conditioning in a different environment. The differential effects of escapable vs. inescapable stress were uncovered soon thereafter. In an important study, Baratta et al. (2007) investigated the effects of stressor controllability on fear learning in wildtype rats. There were three groups of rats. The groups either received escapable (controllable) shock (ES), yoked inescapable (uncontrollable) shock (IS), or were home cage controls. Four experimental paradigms comprised this study.

1) In the first paradigm, the stressor controllability paradigm outlined above was performed on the three groups of rats 7 days before a fear conditioning paradigm that paired shock to an auditory tone in a new environment. Similarly to Rau, DeCola & Fanselow (2005), uncontrollable stress potentiated fear conditioning: the uncontrollable stress group showed greater freezing to the conditioning context and to the conditioned tone (tested in yet a third context) than the other groups. Interestingly, controllable stress attenuated these forms of fear conditioning relative to uncontrollable stress and home cage, as though controllability over stress were a sort of protective factor against learned fear expression.

2) A second experiment administered fear conditioning first, followed 24 hours later by ES/IS or home cage. There were no group differences in conditioning, which was contextual only. One week later, rats underwent fear extinction learning until a threshold was met. Fourteen days later, they were tested for spontaneous recovery in the conditioning environment. Uncontrollable stress rats showed greater fear responses during extinction, and greater spontaneous recovery of fear 2 weeks after extinction. As further evidence of a protective resiliency effect, controllable stress rats showed relatively decreased fear expression during extinction, and did not show spontaneous recovery of fear.

3) Experiment 3 replicated the first experiment but involved a surgical intervention and pharmacological inactivation of medial prefrontal cortex (at the prelimbic-infralimbic border) during ES, IS or home cage. Like experiment 1, fear conditioning was tested 7 days later. Inactivation of this region by the GABA-A (γ-aminobutyric acid subtype A) receptor agonist muscimol during controllable stress negated the protective effects of stressor controllability on subsequent fear learning during auditory and contextual conditioning.

4) A fourth experiment subjected rats to ES, IS or home cage and then tested responsivity to innate (as opposed to learned) fear 7 days later, by exposing the rats to ferret odor. In this case, controllable stress did not protect against fear learning. Fear responses were increased relative to home cage controls in both ES and IS rats.

These experiments provide animal model evidence that, relative to no

stress, uncontrollable stress is a vulnerability factor leading to increased fear expression, while controllable stress is a resilience factor leading to decreased fear expression, during fear conditioning acquisition, fear extinction learning, and recall after extinction learning (Baratta et al., 2007).

c. Evidence for human dACC function in stressor controllability

Drawing the implications for PTSD still closer, Hartley, Gorun, Reddan, Ramirez & Phelps (2014) sought to replicate in humans some of the rat findings of Baratta et al. (2007). Their paradigm consisted of three groups of healthy humans: ES, IS, and no shock controls. Like the rats in Baratta et al. (2007), the human ES and IS groups in Hartley et al. (2014) were yoked so that each IS individual received the exact amount of shocks as an ES individual, the only difference being the ability to turn off the shocks with a simple joystick task. And like the bidirectional effects of the rat study, they found that pre-exposure to inescapable (uncontrollable) stress led to relatively potentiated fear responses and that pre exposure to escapable (controllable) stress led to relatively attenuated fear responses.

Between-group statistics did not reveal group differences during fear conditioning acquisition, possibly because not all controllable stress participants were convinced that they had control over the shocks. However, there was a significant correlation between the subjective perception of controllability and fear responding across all phases of the experiment (conditioning acquisition, extinction learning, and extinction recall). Specifically, controllable stress

participants' rating of response confidence (degree of confidence that they had learned the correct response to terminate the shocks) was negatively correlated with SCR across experiment phases. While this metric was task-specific, a broader personality trait seemed to have been at play as well. As a subjective measure of general stressor controllability, they used the Internal Control Index (Duttweiler, 1984). This is essentially a measure of trait-like perception of locus of control, similar to the "General Control subscale" of the Perceived Controllability Scale (PCS) developed by Kushner, Riggs, Foa and Miller (1992), which is discussed and critiqued below. Such a trait-like measure may reflect a pre-existing vulnerability that, in turn, is reflected in brain (discussed above; see section VB3a, page 88). Interestingly, Hartley et al. (2014) also found that Internal Control Index scores negatively predicted a measure of their instrumental learning. That is, controllable stress participants with a stronger general belief in their ability to control events were actually faster to learn the operant response required to turn off the shocks.

Hartley et al. (2014) also found that controllability effected extinction learning. When comparing late acquisition to late extinction, the controllable stress group had significantly lower SCR, the no stress group had a trend for lower SCR, and the uncontrollable stress group did not differ between their acquisition and extinction. During extinction recall, regression analysis revealed a significant linear effect on fear responses (SCR) such that controllable stress < no stress < uncontrollable stress, with a t-test revealing that uncontrollable stress

exhibited significantly greater SCR than controllable stress. Controllable stress led to absolute extinction of learned fear: within-subject t-tests revealed that, unlike the uncontrollable stress and no stress groups, the controllable stress group's SCR during extinction recall was not significantly different than zero. Group differences in SCR are presented in the accompanying figure.

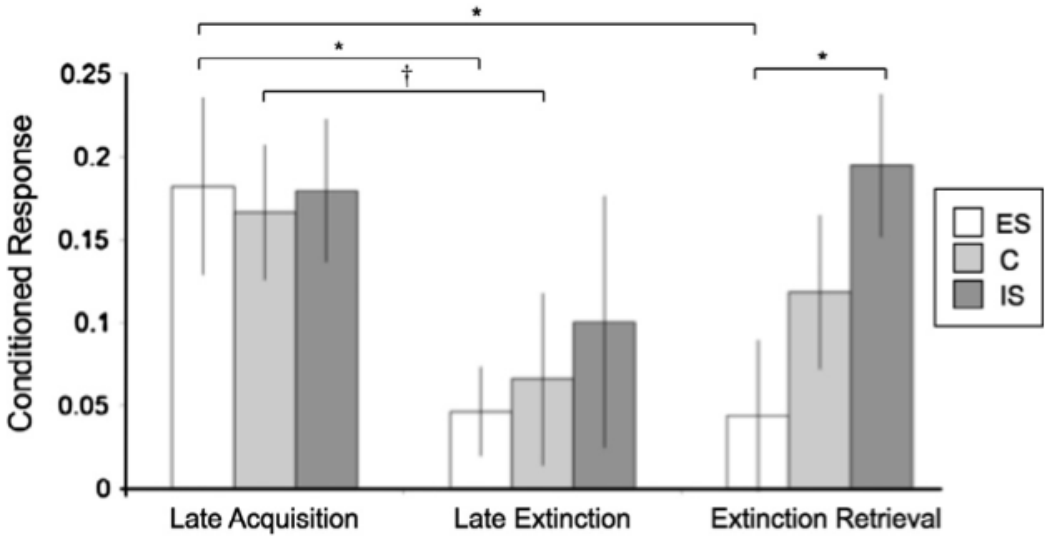


Fig. 2. Mean conditioned responses (CR; skin conductance response to CS+ minus CS−) during late acquisition, late extinction, and a second day extinction retrieval test for participants previously exposed to escapable (ES) or inescapable (IS) stress, and control (C) participants. ES and C participants, but not IS, exhibited decreased CRs during extinction. At day two retrieval test, ES fear expression remained low, C participants showed evidence of spontaneous recovery, and IS CRs increased and were significantly higher than those of ES participants. $^{*}p < .05$, $^{\dagger}p < .1$.

Under Fair Use, reproduced without permission from Hartley, Gorun, Reddan, Ramirez, & Phelps (2014).

d. The serotonin (5-HT) system as an interacting inherited vulnerability

The preceding was an example of how a pre-existing biological trait (hyperresponsitivy and hyperactivity of dACC) could be a vulnerability factor for PTSD. On its own, dACC neurocircuitry dysfunction would increase the likelihood for a traumatic event to be perceived or processed as uncontrollable, thereby increasing that event's conditionability and decreasing its extinguishability, as well as increasing general propensity for exogenous attentional (and possibly memory) capture. Pre-existing dACC neurocircuitry dysfunction could also interact with pre-trauma life experiences such as chronic uncontrollable stress (for example childhood abuse) to further increase vulnerability for PTSD. This is an example of how genetics and/or shared environment may be the source of shared familial vulnerability, what we call a main effect of diagnosis. It is likely that the genetic component of dACC dysfunction is complicated, with many genes interacting to alter the phenotype. However, there is evidence that single genes can confer PTSD vulnerability as well (Koenen, 2007; Pitman et al., 2012; Wilker, Elbert, & Kolassa, 2013). Polymorphisms in the 5-HTTLPR gene (serotonin-transporter-linked polymorphic region, sometimes known as SLC6A4) also regulate the amount of serotonin available at the synapse (Lesch et al., 1996; Lesch & Mössner, 1998), and are associated with a cumulative increased genetic vulnerability to PTSD (Koenen, 2007; Nugent, Amstadter, & Koenen, 2008; Pitman et al., 2012). Furthermore, polymorphisms in this gene explain variance in PTSD-related behavioral endophenotypes. For example, greater amygdala BOLD response to fearful faces has been reported in PTSD (Shin et

al., 2005). The short allele of the 5-HTTLPR gene is associated with attenuated 5-HT transporter protein expression and predicts greater amygdala BOLD response to fearful faces in psychiatrically healthy participants (Hariri et al., 2002). Furthermore, decreased 5-HT transporter protein availability in the amygdala (as assessed by PET scan) also predicts greater amygdala BOLD response to fearful and angry faces in healthy individuals (Rhodes et al., 2007).

Another related behavioral endophenotype is fear conditioning and extinction; 5-HT also influences fear conditioning in both animals and humans (reviewed in (Homberg, 2012)). Knockout genetic mouse models are used to model the 5-HTTLPR s-allele (short allele, as opposed to the l or long allele). 5-HTT knockout mice do not differ from wildtype controls in contextual fear conditioning or in fear extinction, but rather in fear extinction recall (sometimes called fear extinction retention; Homberg, 2012). Interestingly, in some studies, individuals with PTSD also do not differ from healthy controls in fear conditioning or extinction learning but also show impaired fear extinction recall, (Milad et al., 2008; Milad et al., 2009) but see (VanElzakker et al., 2014). In healthy humans, (Hartley et al., 2012) found that, like exposure to controllable vs. uncontrollable stress (Hartley et al., 2014), human serotonin transporter polymorphisms also predict the retention of fear extinction memory.

How could both environmental experience (stressor controllability) and inherited gene confer the same type of vulnerability as a complex trait such as dACC hyperactivity? Not coincidentally, the intersection may be in the

dACC/prelimbic cortex. One of the biological consequences of when dACC/prelimbic - striatum circuitry detects controllability over stress is that separate dACC/prelimbic projections inhibit production of 5-HT in the midbrain (Maier & Watkins, 2005). In accordance with the facilitating effects of 5-HT on learned fear discussed above, this is the mechanism by which the perception of controllability vs. uncontrollability during stress has its effects on fear conditioning and extinction (Maier, 2015; Maier & Watkins, 2010). In accordance with the influence of 5-HT on amygdala activation discussed above, the amygdala is the final target of the circuitry that gives stressor controllability influence over fear conditioning and extinction. In the following section is evidence for the involvement of dACC/prelimbic control over the serotonergic pathway between the dorsal raphe nucleus and basolateral amygdala.

e. Serotonin (5-HT) links stressor controllability to conditioned fear

The dorsal raphe nucleus of the ventral midbrain (mesencephalon) is the largest serotonergic (5-HT) nucleus in the brain. The prelimbic cortex projects to GABAergic cells within the dorsal raphe nucleus, inhibiting its production of 5-HT (Peyron et al., 1998; Vertes, 2004). The dorsal raphe nucleus receives almost all if its cortical input from the prelimbic cortex; in turn, at least in the rat, approximately 10% of dorsal raphe axons project to the amygdala (Ma, Yin, Ai, & Han, 1991). This is indirect evidence that effects of controllability on 5-HT in the amygdala are likely to rely on this pathway. There are several lines of more direct evidence.

In rats, uncontrollable (but not controllable) stress activates 5-HT neurons in the dorsal raphe nucleus (Grahn et al., 1999) and leads to increased 5-HT in the basolateral amygdala, as measured by microdialysis (Amat, Matus-Amat, Watkins, & Maier, 1998). More specifically, the serotonergic cells of the midcaudal dorsal raphe nucleus are preferentially activated by uncontrollable stress and project heavily to amygdala (reviewed in Maier, 2015). In fact, direct pharmacological activation of dorsal raphe 5-HT neurons, even in the absence of stress, mimics the behavioral effects of uncontrollable stress (Maier, Busch, Maswood, Grahn, & Watkins, 1995). Inversely, blocking dorsal raphe nucleus 5-HT production or blocking 5-HT receptors in dorsal raphe projection regions such as basolateral amygdala during uncontrollable stress blocks the predicted behavioral effects of uncontrollable stress (Christianson et al., 2010; Maier et al., 1995; Maier et al., 1993; Maier, Kalman, & Grahn, 1994).

The behavioral effects of uncontrollable stress are long-lasting. The dorsal raphe nucleus is dense with pre-synaptic 5-HT1a autoreceptors (Maier & Watkins, 2005). The inhibitory 5-HT1a autoreceptors on 5-HT neurons are targeted in a paracrine and autocrine fashion and remain desensitized for many days following the 5-HT surge caused by uncontrollable stress (Rozeske et al., 2011). Thus, the normal negative feedback mechanism on 5-HT is lost with repeated uncontrollable stress. This is one potential mechanism for the cumulative effects of chronic stress. Interestingly, these autoreceptors have been found to be decreased in the dorsal raphe nuclei of suicide victims (Arango et al.,

2001), while the density of serotonergic cells and overall size of dorsal raphe was increased in suicide victims (Matthews & Harrison, 2012; Underwood et al., 1999) (however, not all studies have found dorsal raphe size differences in suicide victims). No study has yet investigated 5-HT1a autoreceptor binding in PTSD, although a MDD treatment study including either comorbid PTSD or lifetime PTSD participants found that recent SSRI treatment decreased 5-HT1a binding in a manner that was not correlated with depressive symptom treatment efficacy (Gray et al., 2013).

Genetic variants also predict 5-HT activity, the likelihood of its synaptic reuptake, and the sensitivity of its receptors and autoreceptors, evidencing the intriguing possibility that genetics may explain some of the variance in the propensity to subjectively experience stress as uncontrollable. This is all evidence that serotonin is a key player in the effects of uncontrollable stress on the basolateral amygdala, a primary structure for fear expression which, like the dACC, is consistently hyperresponsive in PTSD. However, it is unlikely that a midbrain neurotransmitter-producing nucleus such as the dorsal raphe, without direct access to cognitive and emotional information or information about bodily state, would be capable of the sorts of calculations necessary to determine whether or not an ongoing experience represents uncontrollable stress. For this, the dACC/ prelimbic cortex, with its integrative properties, is necessary (reviewed above in VB3a, page 88). There is good evidence for the fact that one function of prelimbic cortex in rats is to detect the presence of controllability during stress,

and, if controllability is detected, to inhibit the dorsal raphe's production of 5-HT (Maier, 2015; Maier & Watkins, 2005, 2010).

As mentioned above, the dorsal raphe receives most neocortex projections from the prelimbic cortex/dACC (Peyron et al., 1998). Baratta et al. (2009) conclusively demonstrated the involvement of this circuitry in the detection of stressor controllability through the use of retrograde tracing and immunohistochemistry for Fos in rats undergoing IS vs. ES vs. home cage controls. FluoroGold allows for retrograde tract-tracing because it is taken up by axon terminals and travels back to the originating cell body of neurons; Fos is the protein product of the *c-fos* immediate early gene described earlier (i.e., it is a marker for recent neuronal activity). Baratta et al. (2009) injected FluoroGold into midcaudal dorsal raphe nucleus, which retrogradely labeled the soma of those prelimbic neurons that projected to this region. After yoked stress exposure, in ES but not IS rats, prelimbic cortex neurons were double-labeled with FluoroGold and Fos. This is direct evidence that controllable stress, but not uncontrollable stress, activates those prelimbic neurons that project to serotonergic neurons in the dorsal raphe nucleus. Specifically, prelimbic projection neurons synapse on GABAergic interneurons within the dorsal raphe (Hajós, Richards, Székely, & Sharp, 1998; Jankowski & Sesack, 2004). When the prelimbic cortex detects controllability, there is excitatory glutamatergic projection from the prelimbic cortex to the GABAergic interneurons of the midcaudal dorsal raphe (Amat et al., 2005). When those interneurons are depolarized, 5-HT production within the

dorsal raphe and projection to the basolateral amygdala, is blocked (Maier & Watkins, 2005). Essentially, *all stress causes dorsal raphe nucleus production of 5-HT, including its projection to amygdala, unless the dACC detects the presence of controllability* (Maier, 2015). Taking these empirical findings from the rat literature, one would hypothesize that dysfunctional anywhere in human dACC to 5-HT circuitry could have profound effects for PTSD vulnerability. Again, based on animal models (Baratta et al., 2007) and studies of healthy humans (Hartley et al., 2014; Hartley et al., 2012), one would hypothesize that the inability of PTSD-vulnerable individuals to perceive and process stress as controllable would in turn prime the fear conditioning circuitry to pathological sensitivity in fear conditioning and to deficits in fear extinction learning and recall, as well as promote exogenous attentional capture.

f. dACC/prelimbic cortex is needed to perceive control

To address a potential critique of this model, one seemingly minor distinction should be expanded upon here: prelimbic cortex does not detect *uncontrollable* stress, rather, it detects *controllability*. This relates to the argument made above (section VB, page 76) that, whatever the pre-existing functional abnormalities in dACC represent, all functions of dACC are likely to be effected. If one function of dACC were to detect uncontrollable stress, then a dysfunctional dACC would fail at that task and therefore fail to confer the PTSD-relevant detrimental effects of uncontrollable stress such as exogenous attentional capture and enhanced conditioned fear expression. However, in rodents, the

behavioral effects of uncontrollable stress do not require the prelimbic cortex. Amat et al. (2005) inactivated the glutamatergic pyramidal projection neurons of the prelimbic cortex of rats by activating prelimbic GABAergic interneurons with targeted cannulae injections of the GABA agonist muscimol. In this study, both ES and IS rats showed the detrimental effects of inescapable shock. That is, if prelimbic cortex is taken offline by pharmacological inhibition during uncontrollable stress, rats still show exaggerated conditioned fear, increased measures of anxiety such as lack of exploration, and failure of shuttlebox escape. Thus, a neurocircuitry-related vulnerability to PTSD within dACC would render vulnerable individuals less able to gain the protective effects of controllable stress, while allowing them to be perfectly able to suffer the detrimental effects of uncontrollable stress. This model is a mechanistic candidate by which a main effect of diagnosis on dACC hyperresponsivity could confer actual vulnerability for PTSD upon exposure to a traumatic experience. By this model, dACC vulnerability could interact with 5-HT vulnerability to increase the likelihood that stressors would be interpreted as uncontrollable, or that any beneficial effects of stressor controllability would fail to manifest.

g. dACC/prelimbic stimulation could induce perceived control

Most interestingly for PTSD treatment implications, stimulation of the prelimbic cortex in rats mimics the effects of controllability. In a study by Amat et al. (2008), activating the prelimbic cortex in rats undergoing inescapable tailshock mimicked the effects of stressor controllability. In other words, even though the

stress was uncontrollable, the beneficial effects of controllability were still conferred. This was accomplished by microinjecting the GABA antagonist picrotoxin into prelimbic cortex output cells. Revealing the underlying mechanism for such protective effects, electrical stimulation of rat prelimbic cortex inhibits dorsal raphe 5-HT firing, because prelimbic glutamatergic pyramidal projection neurons synapse on GABAergic interneurons within the dorsal raphe nucleus (Hajós et al., 1998; Jankowski & Sesack, 2004).

This mechanism raises the intriguing translational possibility that exposure therapy in people with PTSD with simultaneous transcranial magnetic stimulation (TMS) of dACC may confer the beneficial effects of stressor controllability while preventing the deleterious effects of lack of control. Exposure therapy can be stressful, and repeated sessions are often necessary to garner therapeutic effects. Simultaneous TMS may endow each session with the beneficial stressor immunization effects of controllability. The TMS settings would be important to calibrate because TMS can either depolarize or hyperpolarize neurons (Rossi, Hallett, Rossini, Pascual-Leone, & Group, 2009). Inhibition of prelimbic cortex in rats blocked the protective effects of stressor controllability (i.e., both IS and ES rats demonstrated the expected behavioral and neurocircuitry consequences of uncontrollable stress; Amat et al., [2005]). This contrast between experimental stimulation vs. experimental inhibition of prelimbic cortex in rats demonstrates the importance of understanding exactly what is represented by the hyperresponsiveness and hyperactivity in the dACC of PTSD-vulnerable humans

(discussed above on page 74, section VA). If hyperresponsiveness and hyperactivity in dACC represent inefficient signaling or ongoing symptom coping, then a "boost" from excitatory TMS may be helpful, but if they represent priming in the form of anticipatory depolarization that harms signal-to-noise, excitatory TMS may harm and inhibitory TMS may help that ratio.

C. STRESSOR CONTROLLABILITY IN INDIVIDUALS WITH PTSD

If stressor controllability is such an important factor in the sensitization of fear conditioning circuitry, one would expect the PTSD literature to prominently feature effective operationalization of "stressor controllability" and that this construct would significantly predict the likelihood of a given traumatic experience to cause PTSD. In the section that follows, I will argue that such effective operationalization has not yet been achieved.

PTSD is unique among psychiatric disorders in that a triggering experience, in addition to post-onset symptoms, is a required criterion for diagnosis. Criterion A-qualifying traumatic events include threat of death or serious injury for self or a loved one. In a nod to stressor controllability, the previous DSM included specific language regarding the experience of control during the precipitating stressor. Specifically, Criterion A2 of the DSM-IV diagnostic criteria (APA 2000) required the subjective experience of the traumatic event to include "fear, helplessness, or horror." While that criterion was found to contribute little to diagnostic validity (Brewin et al., 2009; Brewin et al., 2000;

Kubany et al., 2010) and not included in the DSM-5 (APA 2013), the concept of stressor controllability is likely still a key one for understanding the mechanisms of PTSD. Even if the subjective experience of helplessness during a traumatic experience is neither necessary nor sufficient to explain the emergence of PTSD, lack of behavioral control over a stressor may still explain a significant and large amount of variance in whether a given stressor triggers decompensation into PTSD or not. Some studies have attempted to answer this question.

Kushner, Riggs, Foa and Miller (1992) surveyed 145 female assault survivors in the aftermath of their traumatic experience. They developed and used a new survey, the nine-item Perceived Controllability Scale (PCS). Each item was rated on a 5-point Likert scale. The scale was written to contain three 3-item subscales relating to 1) control during the trauma, 2) perception of control in the future, and 3) general perception of control. They found that general perception of control significantly predicted PTSD symptom severity, in a way that was not dependent upon their measure of trauma severity. Perceptions of control during the assault and perception of control over future assaults did not predict PTSD severity. However, subsequent factor analysis revealed that the three subscales did not split in precisely the way the authors had intended.

Items sharing a Chronbach's alpha of 0.5 or greater were combined into individual subscales. Rather than being split 3-3-3 among the three subscales as the authors had intended, the split was 2-3-5, with one item belonging to both "future" and "general" subscales. The items that the authors called the "General

Control subscale" (i.e., those items that, together, predicted PTSD severity) were really measures of trait-like perception of locus of control. This is an interesting and plausible personality factor that may explain some variance in vulnerability to PTSD following trauma (previous research has found "external locus of control" to predict PTSD vulnerability, e.g., Keane et al. 2006). However, the animal literature is focused on direct experience of control *during* stress, and one would hypothesize that measures of control during stress should predict PTSD.

The two questions comprising the "perception of control during the trauma" subscale are as follows:

> "1) The fact that someone attacked me had nothing to do with my actions.
> 2) All the things that happened to me *during* the attack had absolutely nothing at all to do with my actions."

This subscale appears to be problematic in several ways. Most obviously, the subscale, and the entire scale, is not an over-inclusive item pool. A two-item subscale cannot have good coverage of a psychological construct. Furthermore, even those two items appear to have poor construct validity. Furthermore, these items may conflate self-blame with lack of control. The first question is not even about perception of stressor controllability during the trauma, it is about culpability for being assaulted in the first place. It is about actions preceding the trauma, not emotions during it. So, for example, a soldier who enlisted during wartime should score this item very low - of course they were attacked because they joined the army, flew across an ocean, and entered a combat zone. This speaks very little to the subjective experience during the traumatic event itself:

was the soldier pinned down and unable to escape, did their weapon malfunction in an unrepairable way, did they witness a friend killed before they were able to respond and protect that friend, etc. The second question similarly conflates the possibility of objective influence over a sequence of events with a subjective experience of control. For example, a person may panic and became frazzled during an assault, dropping their phone before they can call 911. Their actions did have to do with the outcome of the event but not because they felt "in control." Another example might be a reflexive response of grabbing tighter or fighting back when a mugger grabs one's purse, and such a response may lead the mugger to strike the victim. In this case, some thing that happened during the attack did have to do with the victim's actions, but the act of fighting back is likely to be negatively and not positively correlated with the subjective experience of control.

Interestingly, one item was written to be part of the "During" subscale but ended up correlating with the "General Control" subscale and therefore predicting PTSD severity. This item was "I had complete control over my emotions *during* the attack (that is, I was able to control how I felt emotionally.)" This, arguably, is the only item in the entire scale that actually did assess perception of control during the attack. Perhaps due to the middling findings, trauma-related stressor controllability psychometrics seem to have largely disappeared since Kushner et al. (1992). This may be due to the scale's apparently poor construct validity. A better-written controllability scale should be developed if the question of incident-

specific stressor controllability in humans is to be addressed.

VI. FUTURE DIRECTIONS

A. OTHER DATA FROM THE TWIN PROJECT

For the twin cohort, the Posner Cueing Task and MSIT were but two parts of a more extensive research program. Therefore, future analyses of the twin data will allow for the aggregation of data from different imaging modalities and other biomarkers. The twin Posner Cueing Task data can be related to structural and functional connectivity studies of relevant attentional circuitry. Diffusion tensor imaging yield data concerning the thickness of fronto-parietal fiber tracts, for example the anterior cingulum bundle. Given that the MSIT is considered a dACC task, there are several ways to correlate MSIT behavioral and SCR results with measures of dACC health and morphology. The same is true with parietal cortex, which other studies have found to be predictably activated during MSIT. Magnetic resonance spectroscopy can inform about the health of dACC, and structural scans can quantify cortical thickness or axon tract thickness. There may be an interesting genetic correlate to MSIT. For example, G allele carriers of mu-opioid receptor gene (OPRM1) show greater dACC activation to social rejection (Rotge et al., 2014). Similarly, MSIT response time could serve as an endophenotype for a known genetic vulnerability to PTSD, such as the *s*hort allele of the serotonin transporter polymorphism. It would be especially interesting if a simple behavioral

measure could serve as a reliable predictor of biomarker abnormalities with a main effect of diagnosis.

B. FUTURE ANALYSES WITH TWIN DATA

There are some problems with the categorical nature of groups in this study. One UxP- individual has civilian PTSD and four ExP+ individuals are in partial remission. This is not particularly problematic given the result of a main effect of diagnosis, and given its interpretation. However, two ExP- individuals have past PTSD. This will need to be reported, and it is possible that they (and their cotwins) should be considered to bear a familial vulnerability factor and moved to the PTSD group. Future analyses will have to attend to these issues. Lifetime CAPS-D may be a better measure than current CAPS-D for correlating with attentional capture.

C. RDoC CATEGORIES

The National Institute of Mental Health (NIMH) has launched a campaign to focus basic and clinical psychiatric research on "research domain criteria" (RDoC) as opposed to psychiatric diagnoses (Insel et al., 2010). Functional brain circuitry relating to the dual attentional system is one of those RDoC domains. One broad future direction of this research is to inform the level to which the DSM diagnosis of PTSD fits the RDoC construct of "sustained threat" within the domain of "negative valence systems" (NIMH, n.d). The current research is evidence that

the "sustained threat" construct overlaps with the "cognitive control" construct, at least for PTSD. Such information could not only provide information about the nature of PTSD, but could also be helpful in determining the value of this new NIMH priority and the extent to which constructs interact.

For example, ADHD (attention deficit-hyperactivity disorder) is a psychiatric vulnerability for PTSD (Adler, Kunz, Chua, Rotrosen, & Resnick, 2004; Antshel et al., 2013; Harrington et al., 2012). Interestingly, like PTSD, ADHD is also associated with dACC and dorsal attention network abnormalities, as well as MSIT task performance abnormalities (Bush, 2011; Bush et al., 2008). There is evidence of increased attentional capture in ADHD during the Posner Cueing Task, although the authors did not make a distinction between EXO and ENDO versions of that task (McDonald, Bennett, Chambers, & Castiello, 1999). Like PTSD, there is some evidence for general executive function abnormalities in ADHD (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). However, ADHD is not generally associated with the type of "sustained threat" symptoms that relate to the dACC functions of fear expression and stressor controllability. It will be interesting and important to resolve the extent to which conditions with dACC dysfunction overlap.

PTSD is a complex and multifaceted condition, and the cognitive abnormalities addressed in the current studies are only one part. But the preceding discussion is an example of how dysfunction in one brain structure can be used to understand relatively diverse symptoms, and to generate related

hypotheses. By synthesizing various literatures (i.e., attention to memory, fear conditioning & extinction, and stressor controllability) and integrating relevant information from those literatures, we may find treatment options that can target those diverse symptoms all at once.

VII. APPENDIX

Table 3. POSNER TASK PARTICIPANTS: Demographic and Clinical Characteristics for Trauma-Exposed (Ex) Participants with (P+) and Without (P-) PTSD and their Trauma-Unexposed (Ux) Identical Co-Twins (ENDO data cohort)

	PTSD Pairs (P+)				Non-PTSD Pairs (P-)				Mixed-Model Analysis of Variance[a]					
	Exposed (N=15)		Unexposed (N=15)		Exposed (N=18)		Unexposed (N=18)		Diagnosis		Trauma Exposure		Interaction	
Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*F*	*p*	*F*	*p*	*F*	*p*
Age (years)	61.47	5.95	61.47	5.95	62.56	3.57	62.56	3.57	0.42	.52	-	-	-	-
Education (years)	13.83	2.53	13.60	3.44	15.42	3.41	14.67	2.59	1.77	.19	1.88	.18	0.52	.48
CAPS														
Re-experiencing (B)	16.73	10.00	2.40	4.30	2.00	4.51	1.00	2.93	**31.11**	**<.001**	**27.31**	**<.001**	**20.65**	**<.001**
Avoidance (C)	19.87	9.69	1.67	4.53	1.50	2.79	0.56	2.36	**53.26**	**<.001**	**50.16**	**<.001**	**40.75**	**<.001**
Hyperarousal (D)	20.40	8.65	1.53	5.94	2.22	3.30	0.39	1.14	**55.66**	**<.001**	**60.51**	**<.001**	**40.97**	**<.001**
Total	57.00	24.28	5.60	14.24	5.72	8.72	1.94	4.09	**60.76**	**<.001**	**60.62**	**<.001**	**45.16**	**<.001**
TLEQ														
Critical Events (CE)[b]	7.14	3.32	5.53	3.48	5.67	2.25	4.67	2.66	1.70	.20	**5.55**	**.025**	0.32	.57
CE, Fear & Horror[b]	3.86	2.96	1.80	1.74	1.72	1.87	1.72	1.87	2.60	.12	**7.41**	**.011**	**7.41**	**.011**
Total Occurrences[b]	21.86	11.51	14.20	13.77	15.67	6.80	10.78	8.96	2.69	.11	**7.35**	**.011**	0.38	.54
CTQ[d]	39.23	10.25	38.29	12.61	37.21	7.81	38.94	10.47	0.003	.96	0.014	.91	0.94	.34
BDI	11.00	9.79	4.00	7.18	4.67	3.85	4.17	3.70	2.99	.094	**7.64**	**.010**	**5.74**	**.023**
BAI	10.27	9.51	2.67	4.27	3.67	5.35	4.89	6.82	1.79	.19	3.59	.067	**6.88**	**.013**
Barratt's[c]	69.07	7.84	58.60	7.67	56.18	10.1	57.76	4.52	**12.93**	**.001**	**4.40**	**.045**	**8.43**	**.007**
WURS[b]	21.13	18.74	10.27	11.18	10.59	11.6	14.94	14.43	0.46	.50	1.54	.22	**8.43**	**.007**
DOSBERT[b]	79.50	19.67	78.20	15.30	80.83	15.9	79.50	15.92	0.05	.83	0.14	.72	0.004	.95
MAST[b]	5.07	5.57	3.27	5.16	2.11	2.49	2.89	3.63	1.43	.24	0.78	.38	**5.52**	**.026**

[a]df=1,31 unless noted otherwise
[b]df=1,30
[c]df=1,29
[d]df=1,27

One individual from each group each left a single item blank in the TLEQ; scores represent total without that item
One P+ pair failed to complete the EXO task

TABLE 4.

Raw EXO	Main effect of diagnosis	F(1,30)=5.63, *p*=.024
	Main effect of exposure	F(1,30)=1.62, *p*=.21
	Interaction	F(1,30)=0.034, *p*=.86
EXO-LOG	Main effect of diagnosis	F(1,30)=9.07, *p*=.005
	Main effect of exposure	F(1,30)=1.05, *p*=.31
	Interaction	F(1,30)=0.415, *p*=.52
EXO trim-1	Main effect of diagnosis	F(1,30)=5.36, *p*=.028
	Main effect of exposure	F(1,30)=0.027, *p*=.87
	Interaction	F(1,30)=0.208, *p*=.65

Twin Posner Cueing Task mixed-model ANOVA table. The main effect of diagnosis on exogenous attentional capture is robust against different forms of data cleaning. EXO-LOG, Raw EXO, and EXO trim-1 all reflect response time difference scores between incongruent and congruent trials in the EXO task. In all cases, lure trials and responses <100msec were excluded. In all cases, the corresponding ENDO analyses were non-significant (*p*s>.1).
Raw EXO = unaltered response times
EXO-LOG = natural log-transformed response times
EXO trim-1 = response times > than 3SD+mean and < mean-3SD were excluded. Two iterations of such trimming led to the exclusion of 25.91%, 21.4%, 7.41% and 7.48% of data points for ExP+ UxP+, ExP- and UxP- respectively and therefore this amount of trimming was deemed excessive.

Table 5. MSIT TASK PARTICIPANTS: Demographic and Clinical Characteristics for Trauma-Exposed (Ex) Participants with (P+) and Without (P-) PTSD and their Trauma-Unexposed Identical Co-Twins (behavioral data cohort)

	PTSD Pairs (P+)				Non-PTSD Pairs (P-)				Mixed-Model Analysis of Variance[a]					
	Exposed (N=10)		Unexposed (N=10)		Exposed (N=12)		Unexposed (N=12)		Diagnosis		Trauma Exposure		Interaction	
Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*F*	*p*	*F*	*p*	*F*	*p*
Age (years)	60.70	6.98	60.70	6.98	62.75	3.98	62.75	3.98	0.75	.397	-	-	-	-
Education (years)	13.80	3.16	14.60	3.75	15.88	3.61	15.17	2.80	0.95	.342	0.01	.919	2.84	.107
CAPS														
Re-experiencing	15.80	9.52	1.10	2.03	1.08	2.23	0.67	2.31	**29.42**	**<.001**	**23.06**	**<.001**	**20.59**	**<.001**
Avoidance	18.80	10.17	0.60	1.90	1.17	2.48	0.83	2.89	**30.97**	**<.001**	**31.75**	**<.001**	**29.51**	**<.001**
Hyperarousal	19.70	7.89	0.00	0.00	1.83	3.04	0.33	1.16	**42.25**	**<.001**	**76.24**	**<.001**	**56.19**	**<.001**
Total	54.30	24.40	1.70	2.98	4.08	7.17	1.83	4.30	**49.60**	**<.001**	**47.59**	**<.001**	**40.10**	**<.001**
TLEQ														
Critical Events (CE)	7.30	3.37	5.90	3.70	5.92	2.27	4.83	2.52	1.28	.270	16.82	.077	0.08	.814
CE with Fear & Horror	4.30	2.95	2.00	1.70	2.17	2.29	1.92	1.68	2.07	.166	**5.61**	**.028**	3.628	.071
Total Occurrences	20.20	10.63	16.40	16.08	16.17	7.02	11.00	7.44	1.74	.202	2.57	.125	0.06	.810
CTQ[b]	36.29	6.97	37.96	13.06	38.55	8.40	37.82	10.86	0.07	.796	0.04	.843	0.26	.615
BDI	10.90	9.86	2.00	2.16	5.00	4.31	3.17	2.86	2.11	.162	**9.95**	**.005**	4.32	.051
BAI	9.40	7.43	1.80	2.82	3.17	1.53	3.17	5.34	2.81	.109	**7.03**	**.015**	**7.03**	**.015**
MAST	6.60	6.52	4.70	6.33	2.33	2.84	3.08	4.06	2.10	.162	0.63	.437	3.34	.082

[a]df=1,22 unless noted otherwise
[b]df=1,19

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