Neural Mechanisms Underlying Attention Deficits in Posttraumatic Stress Disorder

by

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DEDICATION

To all those suffering from mental illness, and to all those with an insatiable curiosity for knowledge.

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ABSTRACT

OBJECTIVE: Post-traumatic stress disorder (PTSD) is associated with altered attentional performance and functional connectivity in intrinsic connectivity networks (ICNs) related to attention. There is conflicting research regarding the specific type of attention impairments present in PTSD as the commonly used tests of attention do not isolate the mechanisms behind attention abnormalities. Additionally, because ICNs are typically measured at rest, it is unclear how altered connectivity may contribute to task performance. Understanding which aspects of attention are affected in PTSD could improve our understanding of the mechanisms by which these deficits influence symptoms, in turn, improving treatment by targeting these processes. **AIM 1:** We sought to characterize the type of behavioral attentional impairment present in PTSD according to Posner and Peterson's tripartite model of attention using the Attention Network Task (ANT). We then examined the association between attention performance and resting-state functional connectivity (rsFC). Male veterans with PTSD were impaired at disengaging spatial attention relative to male community controls and exhibited greater cross-network rsFC of the salience network. Moreover, attention performance was related to rsFC in the control, but not in the PTSD group. However, it remained unclear whether patterns of rsFC are also related to changes in neural function during attention performance as the ANT was completed outside of scanner. We investigated this question in aim 2. **AIM 2:** We examined whether patterns of rsFC were predictive of attention task performance, activity and connectivity across a sample of non-trauma exposed controls, trauma-exposed controls and individuals with PTSD. Across all subjects, we found that ICNs present at rest were predictive of attention task

neural activation, connectivity and behavioral performance. However, the relationships we found were very different depending on the task condition, network node and task measure (i.e. activation vs connectivity). This suggests that resting-state could be an alternative to active tasks to study brain function in psychiatric populations in the future, such that alterations in ICNs at rest in PTSD may be reflective of impairments on an attention task. However, the mechanisms by which ICNs contribute to attention abnormalities in PTSD remained unclear. Additionally, it remained unclear whether alterations of ICNs are specific to PTSD or are partially related to trauma-exposure. We investigated these questions in aim 3. **AIM 3:** We investigated the neural mechanisms underlying attention impairments in PTSD by using the same measures as aim 2. We found that the PTSD group showed deficits in the utilization of spatial information. During cue processing, the PTSD group exhibited salience network intrusions, but during target processing, they showed both a failure to suppress the default-mode network and a greater engagement of attentional control regions. Lastly, trauma-exposed controls showed some behavioral and neural alterations in attention measures. **CONCLUSION:** In this dissertation, we demonstrated that 1) resting-state ICNs are predictive of attention-task measures and 2) spatial attention is disrupted in PTSD. Our results suggest a possible mechanism of attention disruptions in PTSD, by which the salience network interferes with goal-directed attention, resulting in a reduced ability to encode contextual information. This in turn may influence one's propensity for attentional lapses, thus requiring greater engagement of attentional control regions to execute correct responses. Treatments which target these neural networks or cognitive deficits could be a new avenue for PTSD research.

CHAPTER I

Introduction

It is sobering to think that 70% to 90% of the U.S. population will experience a traumatic event in their lifetime (Kilpatrick et al., 2013). While many people recover from such experiences, up to 20% of people who experience a traumatic event develop Posttraumatic Stress Disorder (PTSD) (Alliance., 2001), a disorder characterized by intrusive thoughts, hyperarousal, avoidance and negative alterations in mood and cognition (American Psychiatric Association, 2013). While there are evidence-based treatments for PTSD, these are only effective in some individuals, while partially effective, not effective or not accessible to others (Committee on the Assessment of Ongoing Efforts in the Treatment of Posttraumatic Stress Disorder, Board on the Health of Select Populations, & Institute of Medicine, 2014; Connor, Sutherland, Tupler, Malik, & Davidson, 1999; Hembree et al., 2003; Ipser, Seedat, & Stein, 2006). Thus, there is a great need to better understand the mechanisms underlying PTSD development and maintenance to assist in the development of effective treatments.

A key feature of PTSD is the dysregulation of emotion (Frewen & Lanius, 2006). Effective emotion regulation requires efficient control of attentional processes. Prior findings suggest that ineffective allocation of attentional resources, with a bias to preferentially attend to threatening environmental cues, may contribute to the development and maintenance of anxiety symptoms and disorders (Amstadter, 2008). Further, this bias towards threat may reflect difficulties in shifting attention away from threat cues (Cisler & Koster, 2010).

Many independent lines of investigation have implicated attention abnormalities in PTSD. First and foremost, patients with PTSD describe symptoms of hyperarousalconcentration difficulties and intrusive thoughts (American Psychiatric Association, 2013; VanElzakker, 2016), all of which may be related to attention abnormalities. For example, PTSD patients frequently report lapses of attention, difficulty focusing and becoming distracted (Lew et al., 2011). Second, there is high comorbidity between PTSD and Attention Deficit Hyperactivity Disorder (ADHD) (Hahn, Aldarondo, Silverman, McCormick, & Koenen, 2015). Third, PTSD patients display altered attention biases towards emotional stimuli (Pineles, Shipherd, Mostoufi, Abramovitz, & Yovel, 2009). Finally, PTSD patients have altered performance on neuropsychological tests of attention (Aupperle, Melrose, Stein, & Paulus, 2012; Polak, Witteveen, Reitsma, & Olff, 2012; Qureshi et al., 2011). These findings suggest the potential relevance of attentional control processes to PTSD.

There are, however, substantial conceptual and methodological gaps between the basic and the clinical research on attention in PTSD. First neuropsychological tests commonly used in clinical settings do not isolate the physiological mechanisms behind attention abnormalities and the constructs measured do not map onto the neurocircuits governing attention (Petersen & Posner, 2012). Second, there are conflicting research findings regarding the specific type of attention impairments present in PTSD. This dissertation aims to fill these gaps in our knowledge by integrating multiple research methods to investigate the attentional processes and underlying neural circuitry in PTSD.

What is attention?

According to William James, (James, 1890),

> "Everyone knows what attention is. It is taking possession of the mind in clear and vivid form of one out of what seem several simultaneous objects of trains of thought (pp. 381–382)."

While it may seem obvious what attention is, there are strikingly different definitions in the literature. The first set of definitions stems from the neuropsychology literature, while the second stems from the cognitive neuroscience literature.

Neuropsychology attempts to understand the relationship between behavioral impairments and brain disturbances using a battery of non-invasive tests. Interest in establishing these relationships began in the 19th century when Paul Broca and Carl Wernicke, who were working with language impaired patients, identified specific areas of brain damage in these patients postmortem (Shallice, 1988). However, examining the brain postmortem is rarely feasible. Thus, tests developed by neuropsychologists have been a valiant effort to understand neurobiological processes underlying behavior without directly observing the brain itself. From this, largely functional and essentially hypothetical categories of attention have been postulated, which are still used in clinical neuropsychology today. In this domain (M. Sohlberg & Mateer, 1989), attention is categorized as focused (directing attention to one input) and divided (focusing on multiple inputs simultaneously). Focused attention is further categorized as sustained (attending to one specific task for continuous period of time), selective (focusing on one task while filtering out distractions) and alternating attention (switching focus back and forth between tasks with different demands).

While these distinctions appear to have face validity, they have not been shown to have distinct neurobiological underpinnings as once assumed. According to Patterson and Plaut, neuropsychology "has yielded relatively little advance in understanding how the brain

accomplishes its cognitive business" (Patterson & Plaut, 2009, p. 39). Research in cognitive psychology, has, however, established a model of attention that more closely maps neural functioning. According to Posner & Petersen (1990), attention consists of three components: alerting (maintaining a state of vigilance and attending to novel stimuli), orienting (shifting and focusing on a subset of inputs) and conflict monitoring/executive attention (attention to and resolving incongruent stimuli). Roughly speaking, sustained attention in neuropsychology nomenclature may be thought of as similar to what Posner calls alerting attention, while selective attention may be thought of as similar to what Posner calls orienting attention, however, depending on the object of focus, the clinical components of attention may involve any or all of Posner's components. For example, sustaining one's attention on a task for a long period of time may require vigilance, repeatedly shifting and attention as distractions arise and conflict monitoring to detect the stimuli of interest while ignoring the rest. While alerting is considered to be a stimulus-driven, bottom-up process, meaning that it is automatic and reflexive, orienting attention is thought to be top-down and volitional (Corbetta & Shulman, 2002). Subsequent studies have suggested that these three components likely have distinct neuroanatomy (Petersen & Posner, 2012) that will be discussed in detail in the next section.

Neural circuitry of attention

Posner's attention model

Posner & Petersen (1990) proposed that attention has distinct neuroanatomy that can be divided into three components: alerting, orienting, and conflict monitoring. Early animal and human lesion studies supported this proposal, demonstrating that alerting, orienting and conflict are modulated by different neurotransmitters systems, mainly, noradrenergic, cholinergic and

dopaminergic, respectively. Anti-noradrenergic drugs can block the effects of warning cues (Marrocco & Davidson, 1998) on the alerting system, while lesions to cholinergic systems in the basal forebrain interfere with orienting attention (Everitt & Robbins, 1997; Voytko et al., 1994) and production of dopamine in the ventral tegmental area (Fossella et al., 2002) can modulate the conflict effect. Individual differences in conflict monitoring have also been associated with genetic polymorphisms of dopamine-related genes (Fan, Fossella, Sommer, Wu, & Posner, 2003; Green et al., 2008).

Neuroimaging studies implicate both cortical and subcortical brain areas in the modulation of these attention components. Alerting activates a fronto-parietal-thalamic system of areas in the ventral frontal and parietal cortices, thalamus, and locus coeruleus (Coull, Frith, Büchel, & Nobre, 2000; Fan, McCandliss, Fossella, Flombaum, & Posner, 2005). Orienting activates more dorsal fronto-parietal system including the human frontal eye fields and intraparietal sulcus, as well as subcortical structures such as the superior colliculus (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Fan et al., 2005). The role of these areas in orienting is further supported by single cell recording of neurons in non-human primates (Schafer & Moore, 2007; Thompson, Biscoe, & Sato, 2005). Conflict activates the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (dLPFC) (Botvinick, Braver, & Barch, 2001; Fan et al., 2005), areas, which receive projections from the ventral tegmental area (Botvinick, Cohen, & Carter, 2004).

In sum, there are clear neuroanatomical substrates of Posner's attention components. Furthermore, double dissociations in drug and neuroimaging studies have demonstrated their independence (Fan et al., 2005; Fan, McCandliss, Sommer, Raz, & Posner, 2002; Fernandez-

Duque & Posner, 1997), though these attention components may influence one another, and real-world tasks, likely involve in the interaction of multiple systems (Fan et al., 2009). Thus, examining attention functioning according to this model may elucidate impairment in specific neural circuits. However, neuroscience research using resting-state functional connectivity (rsFC) has also demonstrated that attention may be subserved by several intrinsic connectivity networks which may or may not overlap with Posner's model.

Intrinsic connectivity networks of attention

Functional magnetic resonance imaging (fMRI) studies suggest that the brain might be organized into multiple distinct intrinsic connectivity networks (ICNs), groups of brain regions (Figure 1.1), whose low frequency spontaneous blood-oxygenation-level-dependent (BOLD) activity fluctuates together (Raichle, 2011; Yeo et al., 2011). Broadly speaking, these networks can be grouped into "task-positive," brain areas which are activated during tasks requiring external attentional control and "task-negative," brain areas which are deactivated during task performance, but are instead activated during "rest" a passive, daydreaming-like state (Power et al., 2011). There are three attention-related neural networks that are task-positive, including the salience network/cinguo-opercular network (SN), the ventral attention network (VAN) and the dorsal attention network (DAN) while there is one task-negative network termed the default mode network (DMN) (Corbetta & Shulman, 2002; Ptak, 2012; Seeley et al., 2007) and finally there is one network, termed frontoparietal control network (FPCN), involved in the integration of information from both task-positive and task-negative networks (Markett et al., 2014). The parcellation of these networks was originally described using functional connectivity, a method

which examines the degree to which different brain area's low frequency BOLD activity correlates with one another over time (Yeo et al., 2011).

These networks serve distinct, but related functions in the control of attention. First, the SN, anchored in the anterior insula (AI), amygdala and dorsal anterior cingulate cortex (dACC), is involved in detecting salient stimuli and in signaling the need to switch from a state of rest to a state of task performance and is activated during conflict monitoring tasks (Menon & Uddin, 2010). The VAN, anchored in the right inferior frontal gyrus and right temporoparietal junction, is involved in maintaining tonic alertness and detecting unexpected warning cues (Corbetta & Shulman, 2002). Some investigators suggests that the SN and VAN might be partially overlapping networks (Kucyi, Hodaie, & Davis, 2012; Yeo et al., 2011), although other research shows that they are distinct (Sadaghiani & D'Esposito, 2014). The DAN, anchored in the frontal eye fields, dorsolateral prefrontal cortex and superior parietal lobe, is involved in selective visual and spatial attention (Corbetta & Shulman, 2002). The DMN, anchored in the ventromedial prefrontal cortex, posterior cingulate cortex and hippocampus is involved in states of rest that do not involve exogenous attention to the environment (Buckner & Vincent, 2007). Lastly, the FPCN, anchored in the lateral and dorsal medial prefrontal cortex and the posterior parietal cortex (anatomically between the DAN and DMN), is involved in working memory and guiding goal directed behavior by integrating information from both task-positive and negative networks (Markett et al., 2014).

While the exact number of ICNs reported differs across papers (Power et al., 2011; Yeo et al., 2011), there is a clear consensus that such networks exist (Damoiseaux et al., 2006; Zuo et al., 2010). The presence of such large scale networks are present in children (Solé-Padullés et

al., 2016) and adults (Guo et al., 2012), males and females (Weissman-Fogel, Moayedi, Taylor, Pope, & Davis, 2010), healthy individuals (Damoiseaux et al., 2006) and those with neuropsychiatric disorders (Broyd et al., 2009; Greicius, 2008). Homologs of such networks have also been reported in non-human primates (Mantini et al., 2011) and rats (Lu et al., 2012).

Integration of Posner's model with intrinsic connectivity networks

Although Posner's tripartite model of attention was proposed before the discovery of ICNs, the brain areas involved in the three attention components largely overlap with several ICNs. Alerting, orienting and conflict monitoring activate regions of the VAN, DAN and SN, respectively (Fan et al., 2005), providing further support for the use of this model to study attention functioning. However, the attention components described by Posner are not specific to these networks. Alerting has also been shown to activate the parts of the SN orienting has been shown to activate parts of the VAN, and conflict has also been shown to activate parts of the FPCN (Xuan et al., 2016). Such findings have led to a re-examination of the independence of Posner's attention components and a more detailed understanding of the cognitive processes involved in each. Alerting is now thought to involve the maintenance of both tonic and phasic arousal (Posner, 2008), the former of which may rely on subcortical structures (i.e. thalamus and locus coeruleus), while the latter may also rely on the VAN. Additionally, multiple studies have reported that conflict effects can be modulated by alerting cues (Callejas, Lupiàñez, Funes, & Tudela, 2005; Macleod et al., 2010; Weinbach, Henik, Shofty, Gabay, & Henik, 2013), which may explain why both activate the AI and ACC of the SN. Fan (2014) proposed that both conflict and warning cue monitoring are forms of uncertainty. The activation the SN that is observed in alerting may reflect a baseline monitoring for the presence of warning cues and

response preparation that occurs during states of readiness (Xuan et al., 2016). Activation of the VAN has also been noted during orienting. This occurs when warning cues appear at unexpected locations (Corbetta, Patel, & Shulman, 2008). It is now understood that orienting encompasses the cognitive processes of disengaging attention from the current stimulus, moving and reengaging attention to the new stimulus, the former of which (disengaging) requires the recruitment of the temporoparietal junction of the VAN, while the latter requires the recruitment of the DAN (Corbetta et al., 2008; Fan et al., 2009; Vossel, Geng, & Fink, 2014). Finally, recent accounts of the conflict (Petersen & Posner, 2012) have expanded Posner's model to encompass the functions of both the SN and the FPCN. The original model described conflict as being responsible for monitoring and resolving competing response tendencies in the environment (Posner 1990), which requires SN regions such as the AI and ACC (Thomaes et al., 2012). More recent imaging studies show that the SN interacts with the FPCN to provide moment-to-moment feedback about performance, such that the FPCN can provide top-down control to readjust performance in the future (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Petersen & Posner, 2012).

Overall, Posner's model of attention is largely consistent with the emerging literature on ICNs. While Posner's attention components are not a recapitulation of ICNs, the use of such models in conjunction may enhance our understanding of the cognitive processes involved in attention as well as the neural underpinnings. Such ideas may be useful in studying attention deficits in psychiatric disorders such as PTSD.

Attention deficits in PTSD

Attention Deficit Hyperactivity Disorder and PTSD.

One of the strongest pieces of evidence for attention difficulties in PTSD is the high comorbidity with ADHD (Daud & Rydelius, 2009), a disorder characterized by impulsivity, inattentiveness and hyperactivity (American Psychiatric Association, 2013). This association between PTSD and ADHD goes beyond trauma exposure, or the association seen in general psychiatric illness. In fact, one study found that behavioral performance in those with ADHD was indistinguishable from those with PTSD on a battery of attention tasks (Armengol & Cavanaugh-Sawan, 2003). A recent meta-analysis of 22 studies found that in samples of ADHD, the risk of developing PTSD was four times greater than non-trauma-exposed control (NTC) samples (Hahn et al., 2015). Similarly, in samples of PTSD, the risk of having ADHD was twofold that of controls with similar levels of trauma exposure (Hahn et al., 2015). The relative risk was still significantly higher even when compared to psychiatric populations such as oppositional defiant disorder, mood disorders, antisocial personality, substance use disorders and panic disorder (Hahn et al., 2015). This meta-analysis included studies that used structured diagnostic assessments, included adequate control samples (e.g. non-ADHD) and had a primary focus on the relationship between ADHD and PTSD.

The literature suggests that the link between ADHD and PTSD might be bidirectional. First, ADHD may constitute a risk factor for developing PTSD. Because, ADHD is an early onset psychological disorder, it often precedes a PTSD diagnosis. Those with ADHD also have difficulty with impulse control, focusing and stress management (Szymanski, Sapanski, & Conway, 2011) and are more likely to be perceived as defiant, noncompliant and aggressive (Monastra, 2008). Due to their impulsive behavior, they may be more likely to experience traumatic events (Szymanski et al., 2011). ADHD may also affect the way that fear memories

are consolidated (Adler, Kunz, Chua, Rotrosen, & Resnick, 2004; Storm & White, 2010). Lastly, ADHD may affect neurobiological circuits in a way that makes ones more vulnerable to develop PTSD.

In concert, PTSD may also constitute a risk factor for developing ADHD. For example, trauma-exposed children tend to have trouble regulating anger and difficulty self-soothing (Luxenberg, Spinazzola, Van Der Kolk, Hidalgo, & Hunt, 2001). Trauma may affect the ability of children to express their emotions, resulting in acting out through externalizing behaviors (Szymanski et al., 2011). Symptoms of PTSD may manifest as ADHD or be misdiagnosed as ADHD in children. Specifically, avoidance symptoms may manifest as inattentive ADHD symptoms, hyperarousal as hyperactivity and intrusive symptoms as difficulty listening (Shucard, McCabe, & Szymanski, 2008). PTSD may also affect the neurobiological circuits related to attention, which make one more vulnerable to develop ADHD. To fill the gap in our knowledge of how these two disorders influence one another, future research should examine the common genetic and neurobiological circuits of these disorders, as well as examine longitudinally how specific symptoms confer risk factors at different developmental periods (Hahn et al., 2015).

PTSD performance on traditional neuropsychological tests.

Clinically, attention has been assessed using a battery of neuropsychological tests, in which longer RTs and decreased accuracy reflect deficits in attention. Earlier reviews (Aupperle et al., 2012; Horner & Hamner, 2002) and two more recent meta-analyses of cognitive functioning in PTSD (Polak et al., 2012; Qureshi et al., 2011) have all found evidence for

attentional impairments based on these measures, while evidence for impairments in other cognitive domains, such as memory, learning and visuospatial functioning is much weaker.

Although many neuropsychological tests are purported to measure attention, they do not effectively isolate the measurement of attention from that of other executive functions (Brock & Clinton, 2007; Perry & Hodges, 1999). One such example are memory span tests (e.g. digits span), which ask the participant to immediately repeat a list of items he/she just saw or heard (D. Wechsler, 2008; David Wechsler, 2009). Some studies have found PTSD participants to be impaired on these tests (Koenen et al., 2001; Polak et al., 2012; Samuelson et al., 2006; Steudte-Schmiedgen et al., 2014; Vasterling et al., 2002), while others have not (Burriss, Ayers, Ginsberg, & Powell, 2008; Gil, Calev, Greenberg, & Kugelmass, 1990; Gilbertson et al., 2006; Neylan et al., 2004; Twamley, Hami, & Stein, 2004; Uddo, Vasterling, Brailey, & Sutker, 1993). While attention is required to complete these tasks, they also involve working memory, which is functionally and neuroanatomically distinct from attention (Awh, Vogel, & Oh, 2006). Thus, deficits on these tasks may reflect memory deficits and not attention. This was supported by LaGarde, Doyon, & Brunet (2010) and Johnsen & Asbjørnsen (2008), who only found PTSD participants to have deficits on the backward digit span, which requires greater working memory. A similar story is found with tests that are purported to measure alternating attention (e.g. the Wisconsin Card Sort Task (Berg, 1948), the Tower of London (Krikorian, Bartok, Gay, & Anonymous, 1994), the Trail Making Test Part B (TMT-B) (Gray, 2006) and the digit symbol test (Wechsler, 2008)). While some authors have used impairments on these tests to implicate attention deficits in PTSD (Brandes et al., 2002; Gilbertson et al., 2006; Hart et al., 2008; Jenkins et al., 2010; Kivling-Bodén & Sundbom, 2003; Koso & Hansen, 2006; Lagarde et al., 2010;

Madu & Peltzer, 2000; Polak et al., 2012; Stein, Kennedy, & Twamley, 2002; Sutker, Winstead, Galina, & Allain, 1991), the findings can implicate deficits in other domains besides attention, such as planning, cognitive flexibility and set shifting and a number of studies have failed to find impairments in PTSD (Gil et al., 1990; Kanagaratnam & Asbjørnsen, 2007; Lagarde et al., 2010; Steudte-Schmiedgen et al., 2014; Twamley et al., 2004; Vasterling et al., 2002) . Finally, tests of processing speed, such as The Trail Making Test Part A (TMT-A) (Gray, 2006) in which the subject must connect a series of dots as quickly as possible without sacrificing accuracy, are purported to measure visual attention, but do not isolate the measurement of attention from that of processing speed, which may be independent of attention (Shanahan et al., 2006). While two studies have found impairments in PTSD on this test (Koso & Hansen, 2006; Sutker, Vasterling, Brailey, & Allain, 1995), a number of others have not (Jenkins et al., 2010; Koenen et al., 2001; Lagarde et al., 2010; Stein et al., 2002; Twamley et al., 2004). Therefore, the mixed results in this area may reflect the difficulty in parsing these two constructs apart. In sum, many studies suggest PTSD impairments on these neuropsychological tasks; however, the mechanisms underlying the impairments remain unclear.

A further limitation with neuropsychological tests is that the constructs measured (divided vs focused - sustained, selective and alternating) do not correspond to the underlying neuroanatomy of attention and thus impairments on these tests do not pinpoint specific neural deficits. For example, the division between divided and focused attention is not well supported neuroanatomically (Hahn, Ross, & Stein, 2006). Furthermore, the same tasks (TMT-B, Paced-Auditory-Serial-Addition-Test, digit symbol) that are used to measure divided attention are also purported to measure alternating and sustained attention (Bennett, Raymond, Malia, Bewick, &

Linton, 1998; Jenkins et al., 2010). While all but one study (Gil et al., 1990) has found PTSD participants to have performance deficits on these tasks (Hart et al., 2008; Jenkins et al., 2010; Koenen et al., 2001; Koso, Sarač-Hadzihalilovic, & Hansen, 2012; Lagarde et al., 2010; Madu & Peltzer, 2000; Polak et al., 2012; Stein et al., 2002), the interpretation of these findings in the context of affected neurocircuitry is not yet known.

Cognitive functioning in other domains (memory, learning, etc.) is beyond the scope of this dissertation. While deficits in other cognitive domains have been reported (Bremner, Vermetten, & Vythilingam, 2004; Vasterling et al., 2002; Yehuda, Golier, Halligan, & Harvey, 2004), studies examining these components do not always control for attention functioning (Qureshi et al., 2011). Therefore, it is possible that attention deficits account for these findings, as attention is a requirement for effective memory encoding, learning and retrieval (Qureshi et al., 2011).

Continuous Performance Tasks (CPTs) and response inhibition tasks, on the other hand, are more robust tests for assessing attention deficits. During a CPT, a series of stimuli are presented rapidly and the subject must respond to a target that occurs in low frequency, which requires attention over prolonged periods of time. CPTs are often used in assessing attention in classical attention-related disorders like ADHD (Greenberg & Kindschi, 1994). A number of studies have reported increased RT (McFarlane, Weber, & Clark, 1993) and decreased accuracy (De Bellis, Woolley, & Hooper, 2013; Koso & Hansen, 2006; Semple et al., 1996; Shucard et al., 2008; Vasterling et al., 2002; Vasterling, Brailey, Constans, & Sutker, 1998) in PTSD participants. However, Golier, Yehuda, Cornblatf, & Harvey (1997) reported that PTSD participants only made more commission errors at a trend level, while Stein et al. (2002) and Gil

et al. (1990) reported that PTSD participants, trauma-exposed controls (TEC) and psychiatric controls were all impaired compared to healthy controls, but not significantly different from each other. Furthermore, some studies (Crowell, Kieffer, Siders, & Vanderploeg, 2002; Eren-Kocak, Kilic, Aydin, & Hizli, 2009; Johnsen & Asbjørnsen, 2008; Lagarde et al., 2010; Lindauer et al., 2006; Twamley et al., 2004; Zalewski, Thompson, & Gottesman, 1994) have failed to find evidence for CPT deficits in PTSD. These discrepancies may reflect differences in sample size, study population and PTSD severity. CPTs can require alerting, orienting and conflict monitoring and mixed findings may reflect the fact that PTSD participants are impaired only in specific areas of attention, but not in all three. As a whole, CPTs suggest that attention may be affected in PTSD, but do not isolate the specific type of attention impaired.

Selective attention on a task requires inhibition of prepotent/inappropriate responses (Posner, 1980) and indeed, a number of studies have found PTSD participants to be impaired on response inhibition tasks such as the Haylin Sentence Completion Task (Koso & Hansen, 2006), the Go/No-Go Task (Wu et al., 2010) and the Stop Completion Task (Casada & Roache, 2005). For example, Wu et al. (Wu et al., 2010) reported that PTSD participants made more commission errors on No-Go trials compared to controls, showing that they had difficulty inhibiting their automatic responses. In turn, PTSD participants were faster on Go-trials reflecting a speed-accuracy trade-off. Additionally, Shucard et al. (2008) reported that veterans with PTSD had longer P3 latency and greater frontal P3 amplitude to No-Go and non-target stimuli than controls using ERP. Furthermore, these ERP components were associated with hyperarousal and re-experiencing symptoms. These findings suggest that PTSD participants may have difficulty inhibiting appropriate responses and filtering out non-relevant information.

Ecologically, deficits in response inhibition may manifest as impulsivity, which has been broadly defined as "action without foresight" (Winstanley, Eagle, & Robbins, 2006) and is core diagnostic feature of ADHD (American Psychiatric Association, 2013). Supporting this link are findings that individuals with ADHD manifest response inhibition deficits on tasks such as the Go/No-Go and Stop-Signal Tasks (Patros et al., 2015). Not surprisingly, PTSD and trauma exposure have also been associated with greater impulsivity, further supporting the role of attention deficits in this disorder (Netto et al., 2016). For example, PTSD has been linked to increases in reckless driving (Lapham, C'de Baca, McMillan, & Lapidus, 2006), risky sexual behavior (Green et al., 2005), substance use (Jakupcak et al., 2007), self-harm (Kimbrel et al., 2014) and aggressive behavior (Jakupcak et al., 2007). Furthermore, the significance of impulsivity in PTSD was highlighted by the addition of the symptom "reckless behavior that may lead to accidental injury to self or others, thrill seeking, or high risk behaviors" (American Psychiatric Association, 2013) in the latest edition of the Diagnostic and Statistical Manual of Mental Disorders.

In summary, neuropsychological tests have revealed abnormal cognitive functioning in PTSD. However, such tests have been unable to isolate attention components from one another and from other cognitive processes such as processing speed. They suggest that individuals with PTSD may have difficulty inhibiting appropriate responses and filtering out non-relevant information. Examining attention functioning according to Posner's model may help clarify the nature of attention deficits in PTSD.

Evidence for attention deficits in PTSD according to the Posner model.

In contrast to the neuropsychological literature, there are a number of tests from the cognitive psychology literature (Eriksen & Eriksen, 1974; Fan et al., 2002; Greene et al., 2008; Posner, 1980; Simon & Wolf, 1963; Stroop, 1935) which isolate alerting, orienting and conflict monitoring according to Posner and Peterson's (Posner & Petersen, 1990) tripartite model of attention, which more closely reflects neural circuits of attention (Petersen & Posner, 2012) and therefore, may be more informative in understating attention deficits in PTSD. The only one which measures and isolates all three is the Attention Network Task (ANT; See Figure 2.1) (Fan et al., 2002), which is a combination of the Posner Cueing Task (Posner, 1980) and the Eriksen Flanker Task (Eriksen & Eriksen, 1974). It has been used in a wide variety of populations including children, older adults, individuals with psychiatric disorders and non-human primates (Adólfsdóttir, Sørensen, & Lundervold, 2008; Beran, Washburn, & Kleinman, 2003; Gooding, Braun, & Studer, 2006; Jennings, Dagenbach, Engle, & Funke, 2007). Originally, it was found to have high test-retest reliability, $r = 0.87$ (Fan et al., 2002), but a more recent study found lower split-half reliabilities for the three networks, in addition to small correlations between the three networks, suggesting they are not completely independent (Macleod et al., 2010). However, we are not aware of any superior tests to simultaneously measure these attention components. Since the evidence using the ANT in PTSD is limited to date, we also have tried to address the implications of other findings reported in PTSD related to the alerting, orienting and conflict monitoring components of attention.

Alerting.

Overall while evidence is scarce, there is little evidence for deficits in alerting attention, the ability to maintain a state of vigilance and attend to novel stimuli, in PTSD. On the ANT, the

alerting component is isolated by comparing the RT during trials when there is a temporal warning signal to trials without a temporal warning signal. Only two studies have examined ANT performance in PTSD, with neither finding impairments in alerting attention (Barlow-Ogden & Poynter, 2012; Leskin & White, 2007). Alerting is likely required in most neuropsychological tests, but may be most taxed in sustained attention tasks, such as CPTs and memory span, but as stated earlier the evidence for deficits on CPTs and memory span tests is mixed. Furthermore, CPT and memory span performance may reflect deficits other than alerting. Thus, evidence for alerting deficits is weak, but cannot be ruled out.

Orienting.

Orienting is the ability to shift attention and focus on a subset of inputs (Posner, 1980). Again, it is likely involved in numerous neuropsychological tests, most clearly the Trail Making and digit symbol tests, as the person must visually scan information and move his/her attention to a new spatial location. Interestingly, while impairments for TMT-A are mixed (Jenkins et al., 2010; Koenen et al., 2001; Koso & Hansen, 2006; Lagarde et al., 2010; Stein et al., 2002; Sutker et al., 1995; Twamley et al., 2004), all studies using TMT-B report impairments in PTSD subjects (Hart et al., 2008; Jenkins et al., 2010; Koenen et al., 2001; Koso & Hansen, 2006; Lagarde et al., 2010; Madu & Peltzer, 2000; Polak et al., 2012; Stein et al., 2002; Sutker et al., 1995) and most studies employing the digit symbol test were also positive for PTSD-specific deficits (Brandes et al., 2002; Hart et al., 2008; Jenkins et al., 2010; Parslow & Jorm, 2007). These findings suggest that orienting attention may be impaired in PTSD. However, on tests that directly isolate orienting attention (Posner cueing task; ANT), the findings in PTSD have been mixed. On these tests, orienting is isolated by comparing the RT during trials when there is a

spatial warning signal to trials with a neutral warning signal. Pacheco-Unguetti, Acosta, Marqués, & Lupiáñez (2011) found that patients with anxiety disorders (including PTSD) had greater orienting effects relative to controls, which were driven by greater RT to invalidly cued targets. These findings suggest that the disengagement of attention may be affected in anxiety disorders. . In contrast, . Leskin & White (2007) and Jenkins et al., (2010) did not find orienting deficits in PTSD, while Barlow-Ogden & Poynter, 2012) only found a PTSD+TBI group to have orienting deficits. Between-study differences with regard to the participants (e.g., age, gender, symptom and TBI severity) could potentially account for the observed differences. Moreover, the smaller group size in these studies could have reduced their power to detect group differences with regard to orienting attention. Another possibility is that orienting attention deficits are related to trauma exposure generally and are not specific to PTSD. Clearly, additional research will be needed to clarify the nature of orienting attention deficits in PTSD.

Conflict monitoring.

Impairments in conflict monitoring, or the detection of and resolution of incongruent stimuli in the environment, in PTSD have been mixed. On the ANT, Leskin & White (2007) found PTSD participants to have a larger interference effect than both trauma and non-trauma exposed controls. In addition to the ANT, there are a number of tasks that isolate this process, such as the Stroop (Stroop, 1935) and Simon (Simon & Wolf, 1963) tasks, which compare the RT to respond to a target that is surrounded by incongruent flankers to a target that is surrounded by congruent flankers, termed the interference or conflict effect. A recent meta-analysis found PTSD participants to be impaired on the Stroop task (Polak et al., 2012), while more recently,

Steudte-Schmiedgen (2014) did not find any differences in the interference effect in the Simon Task.

In sum, research has provided evidence that overall attention performance is impaired in PTSD, however, it has not been able to establish which components of attention are affected. At present, the evidence suggests that orienting attention and conflict monitoring may be affected in PTSD, with impaired response inhibition and disengagement possibly contributing to these findings. The evidence for alerting attention is weaker, but cannot be ruled out. Examining neural circuitry might help elucidate these questions, which would be important in understanding how specific PTSD symptoms may be related to attention, thus providing a basis for examining novel treatments.

Abnormalities of intrinsic connectivity networks in PTSD.

As noted earlier, neuroimaging research suggests that the three attention components above (alerting, orienting and conflict monitoring) are influenced by specific intrinsic connectivity networks [23], [31]–[34]. Deficits of attention may therefore be observed in PTSD patients because the disorder disrupts neural networks that are critical for attentional control. However, it is also possible that disruptions of these networks make etiologic or pathophysiologic contributions to the development of PTSD.

ICNs can be studied using resting-state functional connectivity (rsfC), an approach that examines the correlation across time of low-frequency, spontaneous blood-oxygen-level-dependent (BOLD) signals in different brain regions at rest (Yeo et al., 2011). Investigations of resting-state in PTSD have implicated alterations in mainly the SN and DMN (Bluhm et al., 2009; Gong et al., 2014; Kennis, Rademaker, van Rooij, Kahn, & Geuze, 2015; Kennis, van

Rooij, van den Heuvel, Kahn, & Geuze, 2016; Lanius et al., 2010; D. R. Miller et al., 2017; Nicholson et al., 2016; Raji et al., 2015; Sripada, King, Garfinkel, et al., 2012; Yin et al., 2012), with some recent reports of PTSD-related alterations in the VAN (Kennis et al., 2016; Yin et al., 2012; Zhang et al., 2016) and DAN (Gong et al., 2014; Kennis et al., 2016; Zhang et al., 2016). Such PTSD findings raise the possibility that abnormal functioning of ICNs related to attention contributes to attentional impairments in PTSD. The relationship between altered ICN functioning and attention impairments, however, remains unclear.

No PTSD neuroimaging studies have isolated Posner's attention components to study their neural correlates (e.g. there are no imaging studies using the ANT in PTSD), however, a few studies have implicated alterations of brain regions that are part of ICNs in other cognitive tasks. Three studies have found decreased activation (fMRI) and blood flow (PET) to VAN regions in PTSD participants during oddball (Felmingham et al., 2009), Go-No/Go (Falconer et al., 2008) and Stroop tasks (Bremner et al., 2004). In contrast, Bryant et al. (2005) found greater VAN activation, but decreased FPCN activation during an auditory oddball paradigm. Additionally, two of these studies (Bryant et al., 2005; Falconer et al., 2008) found that PTSD participants had greater visual, sensory and motor processing activation, which the authors speculated could have interfered with their ability to maintain attention. There are fewer studies implicating the DAN in PTSD during attention tasks. In one study, patients who exhibited high levels of PTSD symptoms also exhibited decreased DAN activation to attentional targets (Pannu Hayes, LaBar, Petty, McCarthy, & Morey, 2009). In concert, Bryant et al.(2005) reported PTSD participants had decreased right dorsal middle frontal gyrus activation during an auditory oddball task, while the same group (Felmingham et al., 2009) later found increased activity in a

similar, but more posterior area. These studies consisted of relatively small sample sizes, requiring further replication. Lastly, multiple studies have reported SN hyperactivity during cognitive tasks across a variety of attention paradigms including the Stroop (Shin et al., 2007; Thomaes et al., 2012), Multisource interference task (VanElzakker, 2016), auditory oddball tasks (Bryant et al., 2005; Felmingham et al., 2009) and CPTs (Semple et al., 2000), which may intrude upon other neural network's ability to carry-out task-related goals. VanElzakker (2015), however, found that dACC hyperactivity was also present in non-traumatized twins of those with PTSD, suggesting that dACC hyperactivity may be a risk factor for developing PTSD.

Summary

In sum, there have been separate lines of research into PTSD (behavioral, neural activation and functional connectivity), but none have combined these approaches. Each of these methods can provide important information about psychiatric disorders such as PTSD; however, the interpretation is limited unless each method is combined with the other approaches, thereby providing a more enriched understanding of the pathophysiology underlying PTSD.

Methodological strengths and weakness

Before the advent of neuroimaging, behavioral measures were the main methodology for understanding attention (Posner & Petersen, 1990). Research based on behavioral measures, such as the ANT, taught us that attention consists of multiple components (alerting, orienting and conflict monitoring). Furthermore, these components have been shown to have high test-retest reliability (Fan et al., 2002). Applying behavioral measures of attention to psychiatric populations such as PTSD is useful in observing which aspects of daily functioning are affected in the disorder. This is important for understanding a) PTSD symptomatology, b) social and

occupational impairment and c) targets for PTSD treatment. Behavioral measures of attention are limited to measuring reaction time and accuracy differences. They are unable to show the neural mechanisms underlying these processes. For example, individuals may demonstrate the same level of performance on a behavioral task, despite using different neural processes to perform the task. Hence, behavioral measures can provide hypotheses about the neural mechanisms underlying attentional processes, but are unable to directly measure them.

Task-based and resting-state fMRI are two complementary approaches to studying neural circuitry in PTSD. In a task-based study, the BOLD signal is measured for different stimulus types, which are compared to one another using the subtraction method (Capote, 2009). The primary advantage of task-based studies is the ability to map specific cognitive processes to particular brain regions (e.g., identifying the role of the ACC in conflict monitoring (Botvinick et al., 2004)). Another advantage of task-based studies is the ability to examine BOLD responses to particular stimuli of interest. Furthermore, task-based fMRI studies provide information about how such stimuli are processed differently in those with psychiatric conditions relative to control participants. For example, we have learned that PTSD is associated with hyperactivation of emotion generation regions (i.e. amygdala) and hypoactivation of emotion regulation regions (i.e. medial prefrontal cortex) (Etkin & Wager, 2007), which has helped to refine our understanding of emotion dysregulation in PTSD.

Despite the invaluable insights gained from task-based fMRI studies, there may be additional knowledge gained from rsFC that would not be possible with task-based studies. This knowledge includes information about the neural processes that occur in the absence of stimulus elicitation, the neural processes in individuals whose disorders may otherwise impair their task

performance and the functional organization and metabolism in the brain as a whole (Fox & Greicius, 2010).

Unlike typical fMRI tasks, the rest task evokes stimulus independent thought (Buckner & Vincent, 2007). At rest, participants are instructed to relax and let their minds wander while looking at a fixation cross. An advantage of examining functional connectivity between brain areas at rest (such as emotional regulation or attentional control regions) is that we can see how these areas work together in the absence of tasks which may be biased to elicit PTSD symptoms (Sripada, King, Welsh, et al., 2012). Similarly, an inherent limitation of task-based studies is that they are constrained by the performance abilities of the subject. In contrast, the rest task places little demands on the participant, allowing researchers to examine the neural processes of those whose physical or cognitive impairments might otherwise interfere with their ability to perform fMRI tasks (Fox & Greicius, 2010).

Another advantage of rsFC is that it allows for the measurement of large-scale neural networks (i.e. ICNs). At rest, the brain consumes 20% of the body's energy, but task-induced activations may only constitute a fraction of this metabolism (Fox & Greicius, 2010). RsFC provides a method for examining the brain's functional organization and metabolism as a whole. Because task effects may be small, longer acquisition times are required and multiple tasks may be required to study different cognitive processes. Therefore, rsFC saves scanning time by examining multiple neural networks at once. Examining functional connectivity allows us to go beyond the findings of activation studies to understand how brain areas implicated in task-based studies are related to one another. For example, rsFC may help us understand how the amygdala and mPFC are linked in PTSD, possibly contributing to understanding of symptom presentation

or improvement after therapeutic intervention. However, examining ICNs at rest alone is currently limited, because we do not know if the observed differences between patients and controls arise due to differential functional organization of brain areas or because these groups have different cognitive processes in response to the directions of the rest task.

In sum, task-based and rsFC studies may provide new insights into the neural circuitry of PTSD. However, these approaches have largely been applied separately. Combining these approaches could bring about a deeper understanding of the neural mechanisms underlying psychiatric disorders. There is much interest in using rsFC of ICNs to serve as a biomarker in future translational research of psychiatric disorders (Greicius, 2008). In order for rsFC to serve as a useful biomarker, we need to gain a better understanding of how rsFC is related to 1) behavior and 2) task-related activity. This is especially relevant for PTSD and similar conditions that may affect attention-related neurocircuitry, which is thought to be deactivated at rest. Although there is some research to show rsFC is predictive of behavior and task related activity (i.e. during working memory), there has been little research aimed at determining the relationship between rsFC of ICNs and attention-related task activity and behavioral performance.

Specific aims

The primary objective of this dissertation is to use behavioral and neuroimaging data to better understand attentional deficits in PTSD. The central hypothesis is that PTSD is associated with disruptions of neural networks involved in attention, which may underlie difficulty with emotion regulation. This program of research is very innovative in that it is the first to combine attention measures of neural connectivity, activation and behavioral performance in PTSD. The outcome of this work may therefore provide new directions for PTSD research and treatment.

The proposed dissertation will examine the neural basis of attention in PTSD in three experiments.

Specific Aim 1: Experiment 1 aims to characterize the type of behavioral attentional impairment present in PTSD using Posner and Peterson's (Posner & Petersen, 1990) tripartite model of attention and the link between the behavioral measures of attention on ANT and the resting state ICN changes reported in PTSD patients . .

Specific Aim 2: Experiment 2 aims to determine the normative relationship between rsFC of attention-related ICNs, and brain function on an attention task.

Specific Aim 3: Experiment 3 aims to determine the neural mechanisms of attentional impairments in PTSD. Experiment 3 will use the same measures as in Experiment 2 to compare PTSD to trauma-exposed controls and non-trauma-exposed controls. Achieving this aim will contribute to our understanding of the neurobiological basis of PTSD-related attentional abnormalities. Establishing the relationship between task performance and rsFC in a clinical population will help fill the gap in our knowledge about the potential use of rsFC in translational research.

Chapter I Figures

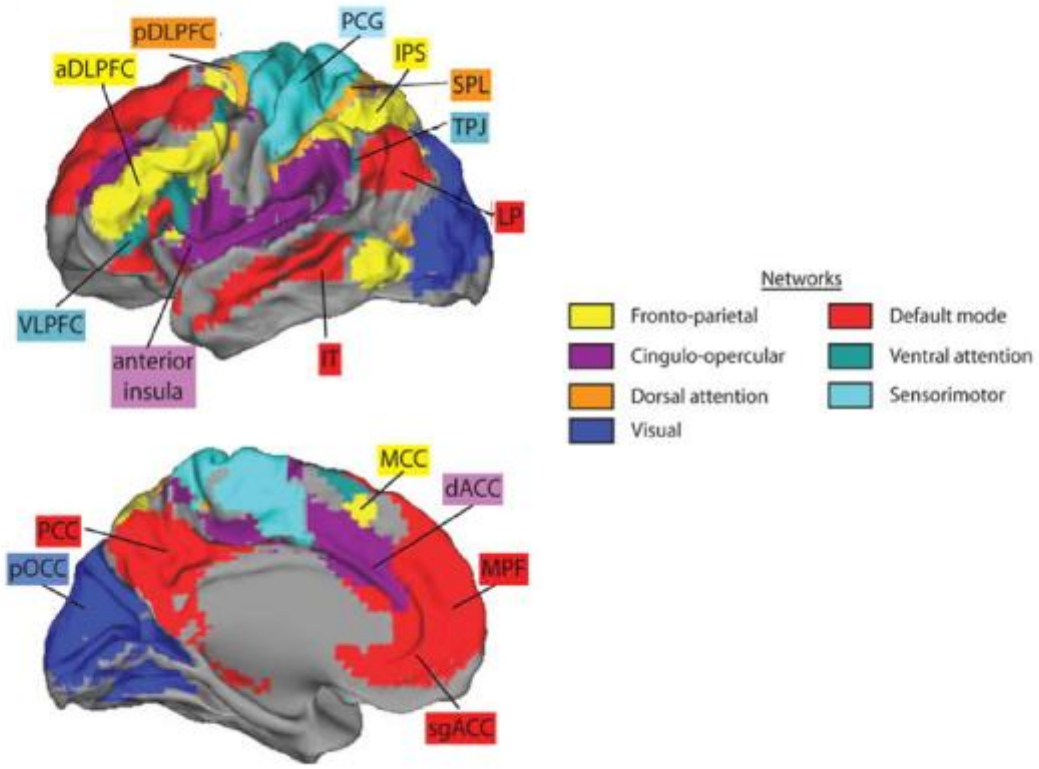


Figure 1.1. *Intrinsic connectivity networks of the human brain.*
PFC, prefrontal cortex; aDLPFC, anterior dorsolateral PFC; dACC, dorsal anterior cingulate cortex; IPS, intraparietal sulcus; IT, inferior temporal cortex; LP, lateral parietal cortex;MCC,middle cingulate cortex; PCC, posterior cingulate cortex; PCG, pre/post central gyrus; pDLPFC, posterior dorsolateral PFC; pOCC, posterior occipital cortex; sgACC, subgenual anterior cingulate cortex; SPL, superior parietal lobule; STG, superior temporal gyrus; TPJ, temporal–parietal junction; VLPFC, ventrolateral PFC. This figure is modified with permission from Sylvester and Corbetta (2012).

CHAPTER II

Experiment 1: Behavioral and neural correlates of disrupted orienting attention in posttraumatic stress disorder

Post-traumatic Stress Disorder (PTSD) is associated with altered attention in multiple domains. For example, PTSD is often associated with altered attentional biases towards threat (Pineles et al., 2009), attentional deficits on neuropsychological tests (Aupperle et al., 2012; Polak et al., 2012; Qureshi et al., 2011) and Attentional Deficit Hyperactivity Disorder (ADHD) (Hahn et al., 2015). Nonetheless, prior research has not characterized which specific types of attention are impaired in PTSD or the underlying neural mechanisms. Understanding which aspects of attention are affected in PTSD could improve our understanding of the mechanisms by which these deficits influence symptoms. This, in turn, could lead to new treatments that target these processes.

Experimental research has identified three important components of attention: alerting, orienting and conflict monitoring (Posner & Petersen, 1990). The alerting component maintains vigilance for novel or unexpected stimuli, the orienting component shifts attention from one item to another and limits focus to a subset of inputs and the conflict monitoring component signals the activation of competing response tendencies. These three components of attention can be isolated using the Attention Network Task (ANT) (Fan et al., 2002).

To date, only two behavioral studies have examined the ANT in PTSD, one reporting deficits in conflict monitoring (Leskin & White, 2007) and the other reporting deficits in orienting attention (Barlow-Ogden & Poynter, 2012) . Other cognitive tests such as the Stroop Task, the Trail Making Test and the Continuous Performance Test also suggest deficits in orienting and conflict monitoring, although the results are mixed (De Bellis et al., 2013; Eren-Kocak et al., 2009; Jenkins et al., 2010; Johnsen & Asbjørnsen, 2008; Lagarde et al., 2010; Polak et al., 2012; Shucard et al., 2008; Steudte-Schmiedgen et al., 2014; Vasterling et al., 2002). Because some neuropsychological tests do not effectively isolate these components of attention from other executive functions or from each other, (Brock & Clinton, 2007; Perry & Hodges, 1999) interpreting their findings as indicating conflict monitoring and orienting attention deficits is challenging. Additionally, many such studies do not integrate clinical findings with the functional neuroanatomy of attention (Qureshi et al., 2011; Weierich, Treat, & Hollingworth, 2008). As a result, there is a gap in our knowledge regarding the neuroanatomical bases of attentional deficits in PTSD.

Of importance in this regard, neuroimaging studies of the Attention Network Test confirm that each component – alerting, orienting and conflict monitoring – is associated with a distinct set of brain regions. Thus, this task could provide an important tool for determining the neuroanatomical bases of attentional deficits in PTSD. Further along these lines, the brain regions that have been linked to each of the three attentional components in the Attention Network Task can be separated into distinct intrinsic connectivity networks (ICNs): groups of brain regions whose low-frequency spontaneous BOLD oscillations fluctuate together at rest (Raichle, 2011; Yeo et al., 2011). For example, the ventral attention network (VAN) is thought

to be involved in alerting, the dorsal attention network (DAN) in orienting and the salience network (SN) in conflict monitoring (Cao et al., 2008; Fan et al., 2005; Muto et al., 2012; Thiel et al., 2004; Westlye et al., 2011). Intrinsic connectivity networks are most readily identified at rest when there is no task-related activity to "obscure" slow wave oscillations, or complex task instructions (Fox & Greicius, 2010). Intrinsic connectivity networks are nonetheless thought to be informative about how functional connections between different brain regions contribute to task performance (Mennes et al., 2010).

Because intrinsic connectivity networks can be effectively probed using resting-state functional connectivity (rsFC), there has been a recent growth in number of investigations on rsFC in PTSD. These studies have implicated alterations in the mainly the salience (Gong et al., 2014; Kennis et al., 2015, 2016; Nicholson et al., 2016; Sripada, King, Garfinkel, et al., 2012; Sripada, King, Welsh, et al., 2012; Tursich et al., 2015; Yin et al., 2012; Zhang et al., 2015, 2016; Zhou et al., 2012). Comprised of the dACC, insula and amygdala, the SN is involved in detecting salient stimuli and in switching from a state of rest to a state of task performance (Seeley et al., 2007). Regions of the SN are also thought to be involved in attentional control during task performance (Seeley et al., 2007). For example, it has been suggested that the dACC performs conflict monitoring, which modulates attention to goal-relevant stimuli (Botvinick et al., 2004).

Some recent investigations have also reported PTSD-related alterations in the ventral (Kennis et al., 2016; Yin et al., 2012; Zhang et al., 2016) and dorsal attention networks (Gong et al., 2014; Kennis et al., 2016; Zhang et al., 2016). The VAN is a closely related and some believe, partially overlapping network with the SN (Kucyi et al., 2012), comprised of the right

ventral lateral prefrontal cortex (just anterior to the insula of the SN) and the temporal parietal junction (TPJ) (Sylvester & Corbetta, 2012). It is also activated when behaviorally relevant stimuli occur unexpectedly (Vossel, Weidner, Driver, Friston, & Fink, 2012). The DAN is comprised of the bilateral posterior dorsal lateral prefrontal cortex, the frontal eye fields and the posterior parietal lobe (Corbetta & Shulman, 2002). It is involved in the voluntary orientation of spatial attention (Vossel et al., 2012). Such PTSD findings raise the possibility that abnormal functioning of ICNs related to attention contributes to attentional impairments in PTSD. The relationship between altered ICN functioning and attention impairments, however, remains unclear.

Behavioral studies suggest that orienting or conflict monitoring may be affected in PTSD, while rsFC implicate alterations in the SN, and possibly other ICNs related to attention. To resolve the discrepancy between these two lines of research, we sought to study behavior attention performance and resting-state connectivity with the same individuals. First, we sought to determine which aspects of attention are altered in veterans with PTSD compared to community controls. Second, we sought to determine whether relationships between behavioral measures of attention and resting-state functional connectivity in attention-related intrinsic connectivity networks differed between PTSD patients and community controls.

Materials and methods

Participants

The study was approved by the Institutional Review Boards at the University of Michigan and the Ann Arbor VA. We obtained written informed consent after providing a complete description of the study to participants.

We recruited male combat (Iraq or Afghanistan) veterans with PTSD (*N*= 49) seeking treatment at the Ann Arbor VA (Table 2.1). Thirteen individuals were ineligible for scanning, or were lost to follow-up, leaving 36 to participate in the neuroimaging component of the study. Current PTSD diagnosis was based on DSM-IV criteria, as assessed by the Clinician Administered PTSD Scale (CAPS) using the frequency + intensity ≥ 4 scoring criteria (Blake et al., 1995). Comorbidity was assessed using the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Those with psychosis, Bipolar I, personality disorders, or suicidal risk were excluded. Participants on psychiatric medications were required to be on a stable dosage for four weeks prior to the fMRI scan. TBI status was established based on the computerized patient record system with a formal consultation at dedicated TBI clinics, or service connection for TBI/postconcussive syndrome.

We recruited age-matched male community controls (*N*=26) via flyers, Craigslist and the University of Michigan clinical studies registry. All controls were free of any Axis I diagnosis (CAPS ≤ 20 and negative MINI) and psychiatric medications. Individuals with a lifetime history of psychosis or bipolar disorder were excluded. Five individuals did not return for the fMRI portion. Thus, only 21 controls underwent neuroimaging. Since the controls were community volunteers, no medical charts for them were available and TBI status could not be assessed.

We were adequately powered to detect group differences on the Attention Network Task. Based on previously reported effect sizes (Leskin & White, 2007), a sample size of 18 people per group would give 80% power to detect group differences at an alpha level of 0.05. The sample sizes of both of our groups were larger than 18.

There were no differences in age, gender, race, education level, mTBI status or medication use between those lost and those not lost to follow up ($p > 0.1$ in all cases). As often happens (Fischer, Dornelas, & Goethe, 2001), there was a significant difference in PTSD symptom severity, with those lost to follow up in the PTSD group reporting higher levels of PTSD symptoms ($M = 89.77$, $SD = 14.56$) than those not lost to follow up ($M = 72.57$, $SD = 14.44$), $t(47) = 3.164$, $p < 0.01$.

Measures

Attention Network Task (ANT). The ANT (Fan et al., 2002), which was performed outside of the fMRI scanner for this study, is a combination of the Posner Cueing Task (Posner, 1980) and the Eriksen Flanker Task (Eriksen & Eriksen, 1974) that probes three components of Posner and Petersen's, 1990 model of attention: alerting, orienting and conflict monitoring (see Figure 2.1). The ANT has high test-retest reliability, $r = 0.87$ (Fan et al., 2002) and has been used in a wide variety of populations including children, older adults, individuals with psychiatric disorders and non-human primates (Adólfsdóttir et al., 2008; Beran et al., 2003; Gooding et al., 2006; Jennings et al., 2007). Each trial of the ANT contains a cue followed by several arrow stimuli. Between 400 and 1600 ms after the start of the trial (which consists of a fixation cross), one of four cue types appears on the screen for 100 ms: a center cue, a double cue, a spatial cue, or no cue. The center cue is a single asterisk that appears at the location of the fixation cross. The double cue consists of two asterisks that appear simultaneously, one above the fixation cross and one below. The spatial cue is a single asterisk that appears above or below the fixation cross. Finally, on trials with no cue, an asterisk is not presented. Spatial cues indicate

where the upcoming arrows will appear while double and center cues indicate the arrows are about to appear, but do not indicate their location. Four-hundred ms after the cue disappears, a row of five arrows appears either above or below the fixation cross. The participant's task is to determine whether the central target arrow points left or right. The central arrow is flanked by four arrows (two at each side) that all point in the same direction as the central arrow (congruent trials) or in the opposite direction (incongruent trials).

All trials of the ANT were performed on a stationary computer (16.5-inch monitor) positioned on a desk free of other objects. Three blocks of five minutes each were preceded by a two-minute practice session. We employed E-prime (Psychology Software Tools, Pittsburg, PA) to present the stimuli and measure trial-specific RT and accuracy.

MRI scanning. Participants underwent structural and functional MRI scanning within two weeks after completing the ANT. The fMRI session included an 8 minute resting-state scan followed by separate emotion regulation tasks (King, Block, Sripada, Rauch, Porter, et al., 2016). During the resting-state scan, a white fixation cross on a black background was displayed at the center of the screen. Participants were told to relax, let their minds wander and keep their eyes fixated on the cross.

MRI data acquisition. MRI data was acquired using a Philips 3 Tesla MRI scanner (Phillips Medical Systems andover, Massachusetts) at the Ann Arbor VA. We acquired 240 T2*-weighted echo planar gradient-recall echo volumes (echo time=30ms, repetition time=2000ms, 64x64 matrix, flip angle=90 degree, field of view=22cm, 42 contiguous 3mm axial slices per volume). Five additional volumes were discarded at the beginning of each run to allow for equilibration of the MRI signal. We also obtained a high-resolution T1-weighted

structural image (3D turbo-fast-field-echo, 1mm isotropic voxel, 256^2 matrix, 180 slices, repetition time=9.8ms, echo time=4.6ms, flip-angle=8 degrees) to provide for more precise anatomical localization.

Data analyses

Demographics and behavioral data. T-tests and chi-square tests were used to assess group differences in age and education level. Attention components across groups were compared using repeated-measures ANCOVAs controlling for education level. The alerting effect is calculated as mean reaction time (RT) in no cue trials minus mean RT in double cue trials (Fan et al., 2002). The orienting effect is calculated as mean RT in central cue trials minus mean RT in spatial cue trials. The conflict effect is calculated as mean RT in incongruent trials minus mean RT in congruent trials. We also examined the effects of mTBI and medication status on ANT effects within the PTSD group. Finally, we used an ANCOVA to test for group differences in accuracy, controlling for education level.

MRI data analyses. MRI data were analyzed using the statistical parametric mapping software package, SPM8 (Wellcome Department of Cognitive Neurology, London, UK). Functional slices within each volume were sinc-interpolated, weighted in time, slice-by-slice, to correct for the staggered sequence of slice acquisition. The functional volumes were then realigned to correct for head motion, spatially normalized to a standard template based upon the Montreal Neurological Institute (MNI) reference brain and smoothed using an 8-mm FWHM Gaussian kernel.

To control for non-neuronal noise sources due to heart beat, respiration and motion (Lund, Madsen, Sidaros, Luo, & Nichols, 2006), we first extracted the average BOLD time series

from structural MRI-derived white matter and cerebrospinal fluid masks. A PCA was performed and the top five components of the time series were added to the model as nuisance covariates. Motion parameters and their first derivatives were also used as nuisance covariates. To control for such micro-movements (Fair et al., 2012) we performed motion scrubbing (removal of volume) using a framewise displacement lever arm of 50 mm, a framewise threshold of 0.5 and a scrub window of 0 frames before and after the target frame (Power, Barnes, & Snyder, 2012; Satterthwaite et al., 2012). Finally, we included an over-scrubbing threshold of 60% (Fair et al., 2012). Motion parameters (maximum and mean framewise displacement) for the two groups were compared via independent-samples t-tests. No global-signal regression was performed to avoid spurious anti-correlations (Anderson et al., 2011), but the data were band-pass filtered in the 0.01 to 0.10-Hz band range (Fox et al., 2005).

Attention Network Task x resting-state functional connectivity analyses. We limited ANT x intrinsic connectivity network analyses to ANT effects that were significantly different between the groups. Prior research has linked the alerting, orienting and conflict monitoring effects to the VAN, DAN and SN, respectively (Petersen & Posner, 2012). We thus examined the interaction among each attentional component, the respective ICN connectivity (using an ICN seed) and group status, using a generalized linear model in SPM (e.g. orienting effect x dorsal attention network seed connectivity x group status). In other words, we examined the link between each ANT effect and resting state functional connectivity in the associated ICN and then assessed group differences in the strength of this link. Seed coordinates were based on DeLuca et al., 2006, because this network parcellation includes coordinates for all ICNs of interest (Table 2.2). Findings were small volume corrected within an ICN search mask (De Luca, Beckmann,

De Stefano, Matthews, & Smith, 2006) using a family-wise-error (FWE) correction at the cluster level with a voxelwise threshold of $p = 0.005$ uncorrected. Lastly, we repeated ANT x ICN analyses excluding those in the PTSD group who had mTBIs to determine if the observed findings were influenced by mTBI.

To assess the potential contributions of aberrant salience network connectivity reported previously in PTSD to attentional deficits in our study, we examined the association between dACC resting-state functional connectivity, ANT scores and group status using a generalized linear model in SPM for any ANT effect in which behavioral group differences had been observed (e.g. the association with of dACC resting-state functional connectivity and orienting and/or alerting). The results were thresholded voxelwise at $p = 0.005$ uncorrected and then, subsequently, at $p < 0.05$ (FWE) at the whole brain cluster level. Ten millimeter spheres around significant interaction peaks were extracted to determine the directionality of the association within each group (connectivity was averaged across all voxels within each sphere). Within the PTSD group, we calculated Bonferroni-corrected Pearson correlations between CAPS subscale scores (intrusive, hyperarousal and avoidance symptoms) and a) significant interaction peaks and b) ANT effects. Functional connectivity foci were labeled by comparison with the Anatomical Automated Labeling atlas in SPM8 (Tzourio-Mazoyer et al., 2002). Voxel coordinates are reported in MNI space.

Results

Demographics

Demographics are reported in Table 2.1. The control group reported higher education levels than the PTSD group. Therefore, level of education (ordinally coded) was used a covariate

in the analyses below. Half of the control group (N = 13) reported experiencing a traumatic event, however none met PTSD criteria on the CAPS (≤ 20). Approximately one third of the PTSD group (N = 18) met criteria for mTBI. Those with mTBI (M=83.33, SD = 18.28) had greater CAPS scores than those without mTBI (M=73.57, SD = 17.55) at a trend level, $t(46) = 1.838$, $p = 0.072$. There were no differences in CAPS subscale scores between those with and without mTBI ($p > .12$) Approximately three quarters of the PTSD group was taking psychiatric medications (N = 38). Those on medications (M = 32.05, SD = 7.87) had greater levels of CAPS avoidance symptoms than those not on medications (M = 25.45, SD = 7.75), $t(46)= -2.45$, $p = 0.018$, but there were no group differences in intrusive, hyperarousal or total CAPS scores, $p > 0.34$ in all cases.

ANT Results

Conflict monitoring. There was no significant group difference in the magnitude of the conflict effect, $p = 0.16$ (Table 2.3; Figure 2.2). In the control group, there were no differences in the magnitude of the conflict effect between those had experienced a traumatic event and those who had not ($p = 0.57$). There were no differences within the PTSD group on conflict monitoring between (a) those with and without mTBI ($p = .758$) and (b) those taking and not taking psychiatric medications, ($p = 0.47$)**.**

Alerting attention. There was no significant group difference in the magnitude of the alerting effect, $p = 0.36$ (Table 2.3; Figure 2.2). In the control group, there were no differences in alerting performance between those had experienced a traumatic event and those who had not ($p = 0.73$). Those taking psychiatric medications (M = 45.34, SD = 25.00) were less alert (larger alerting effect) than those not taking medications (M = 29.19, SD = 32.68) at a trend level, t(49)

= -1.759, p = 0.085. There were no differences within the PTSD group on alerting performance between those with and without mTBI (p = .39).

Orienting attention. The PTSD group showed a larger orienting effect compared to controls (diagnosis by cue type interaction, $F(1,72) = 6.31$, p = 0.014, Table 2.3; Figure 2.2). Tests of simple effects revealed a significant difference in RT between the groups in center cue trials (76.32 ms), $F(1,72) = 5.644$, p = 0.020 and a trend level difference in spatial cue trials (60.72 ms), $F(1,72) = 3.624$, p = 0.061. To control for potential effects of group differences in mean RT on the whole task, we expressed orienting as a percentage of mean RT. The effects remained significant with larger orienting effects in PTSD, $F(1,72) = 4.899$, p = 0.030, driven by slower RT in the center ($F(1,72) = 7.462$, p = 0.008), but not in the spatial (p = 0.365) cue trials, Additionally, there remained a significant group difference in the orienting effect even after removal of the 18 PTSD patients with mTBI, $F(1,54) = 7.605$, p = 0.008.

Because of the individual differences observed in the orienting effect in the PTSD group, we examined if there were similar individual differences in the controls by conducting a median split, resulting in a "large orienting effect" (58.31 ms) and a "small orienting effect" (15.51 ms) group. We then used an independent samples two-tailed t-test to compare the two groups and found that those with larger orienting effects were significantly slower to respond in center cue trials, $t(25) = -2.062$, p = 0.05, compared to the those with smaller orienting effects, but there was no difference between the groups in their RT in spatial cues trials, $t(25) = -1.027$, p = 0.314. In the control group, there were no differences in orienting performance between those had experienced a traumatic event and those who had not (p = 0.81).

Those with mTBI (M=83.33) had greater CAPS scores than those without mTBI (M=73.57) at a trend level, $t(46) = 1.838$, $p = 0.072$. When controlling for mean RT, the mTBI group had a smaller orienting effect than those without mTBI at a trend level, $t(47) = -1.943$, $p = 0.058$, driven by significantly slower RT to spatial cue trials, $t(47) = 2.456$, $p = 0.018$, but not to center cue trials, $t(47) = -0.070$, $p = 0.944$. There were no differences in orienting effect between those taking and those not taking psychiatric medications ($p = .79$)

Accuracy. There were no significant group differences in accuracy, $p > 0.20$ (Table 2.4).

MRI results

Three participants were excluded from the final fMRI analyses due to technical problems in data acquisition (one control and one PTSD subject) and excessive head movement (one control). There were no group differences in head movement, $p > 0.1$ for all parameters. Since we found significant group differences only in orienting attention, the subsequent ANT-ICN analyses involved only the association between the orienting effect and 1) DAN connectivity and 2) SN connectivity.

DAN connectivity and the ANT orienting effect. Because the DAN is thought to play a key role in orienting attention (Corbetta & Shulman, 2002), we examined the interaction between the orienting effect, group status and DAN connectivity, employing a seed in the middle frontal gyrus (MFG) (De Luca et al., 2006). We found a significant group x orienting effect x MFG-amygdala interaction. In controls, the orienting effect increased with cross-network functional connectivity between the MFG and the SN (right amygdala). In the PTSD group, however, there was no such correlation (Table 2.5; Figure 2.3). On the other hand, the PTSD group displayed

greater resting-state functional connectivity between the MFG and the right amygdala without ANT regressors.

There was still a peak in the right amygdala after excluding individuals with mTBI in the PTSD group from the group x orienting x MFG interaction analysis, $p = 0.068$; this peak no longer reached conventional levels of significance, likely because this analysis excluded more than a third of the PTSD group.

SN connectivity and the ANT orienting effect.

We also examined whether salience network connectivity (dACC seed) correlated with the magnitude of the orienting effect. Across all participants, the orienting effect increased with cross-network functional connectivity between the dACC and the VAN (left middle/superior temporal gyrus). However, separate group analyses showed that this was driven entirely by the control group (Table 2.6). Indeed, there were multiple significant group x orienting effect x dACC connectivity interactions that were driven by the control group exhibiting stronger relationships between the orienting effect and cross-network connectivity than the PTSD group. More specifically, in the control group, the orienting effect increased with cross-network functional connectivity between the dACC seed and 1) the DAN and 2) the DMN. In contrast, in the PTSD group the orienting effect decreased with cross-network connectivity between the dACC seed and the DMN (vmPFC; Figure 2.4; Table 2.6). The peaks from these interactions remained in the vmPFC ($p = 0.002$ FWE), left superior frontal gyrus ($p = 0.281$ FWE), right superior frontal gyrus ($p = 0.459$ FWE), left superior temporal gyrus ($p = 0.079$ FWE) and right superior temporal gyrus ($p = 0.213$ FWE), after excluding individuals with mTBI in the PTSD

group; however, the significance of these effects was reduced, likely because this analysis excluded more than a third of the PTSD group.

To better understand the negative relationship between resting-state functional connectivity and the orienting effect in the PTSD group, we examined variability in these measures using PTSD symptom severity on the CAPS and mTBI status. We found a positive correlation between dACC-vmPFC resting-state functional connectivity and intrusive symptoms within the PTSD group, $r(34) = 0.337$, $p = 0.05$ (there was no such correlation involving other CAPS subscales, $p > 0.6$ in all cases). The orienting effect was also negatively correlated with the CAPS intrusive symptoms subscore (controlling for mean RT, $r = -0.380$, $p = 0.008$). This correlation was driven by the fact that those with greater levels of intrusive symptoms were slower to respond in spatial cue trials ($r = 0.396$, $p = 0.005$), but not in center cue trials ($r = -0.103$, $p = ns$). Participants in the PTSD group with mTBI, who had higher CAPS scores than those without mTBI, also displayed slower RT in spatial cue trials.

Group Differences in SN and DAN connectivity without ANT regressors. To determine if the lack of association between the orienting effect and cross-network connectivity in the PTSD group was reflective of a ceiling effect of cross-network connectivity, we further interrogated the SN (dACC seed) and the DAN (MFG seed) connectivity without attentional regressors. To this end, we extracted the time-course of 10-mm-spheres centered at the six peaks of significant SN group differences that were correlated with the size of the orienting effect (mPFC, PCC, left and right superior frontal gyrus, left superior temporal gyrus and right middle temporal gyrus; see Table 2.6). We then examined group differences in ACC connectivity involving these regions. We found that the PTSD group exhibited greater connectivity between

the SN (dACC seed) and four of these regions (mPFC, PCC, R superior frontal, L superior temporal); however, this effect only reached statistical significance at the peak level for the mPFC ([15,38,4], $k = 1$, $z = 3.04$, $p = 0.05$ FWE corrected peak level, $p = 0.115$ cluster level).

We next interrogated MFG connectivity in the amygdala without attentional regressors. We extracted the time-course of the right anatomical amygdala due to the significant group differences in this region that were correlated with the orienting effect (see Table 2.5). We then examined group differences in MFG connectivity within this region. We found that the PTSD group exhibited greater connectivity between the MFG and the right amygdala, ([24,5,-17], $k = 7$, $z = 3.04$, $p = 0.038$ FWE corrected). Lastly, we found no group differences in the ranges of any of the above measures (cross network connectivity and orienting effects). In summary, while the PTSD group showed greater connectivity and orienting effects, there was still a sufficient range to observe progressive relationships in these variables. Thus, a ceiling effect alone does not explain the lack of associations observed in the PTSD group.

Discussion

The present study yielded two findings that inform our understanding of PTSD. First, relative to age-and-gender-matched controls, PTSD participants exhibited greater orienting effects (which were driven by slower responses to central cue trials). Second, in control but not PTSD participants, cross-network connectivity was associated with greater ANT orienting effects. These findings suggest that the processes underlying the ability to orient spatial attention might be altered in PTSD. To our knowledge, this is the first study to examine relationships between neurocognitive measures of attentional performance and rsFC in PTSD.

Attentional performance and PTSD

The larger orienting effect we observed in PTSD could reflect 1) a reduced ability to disengage from the center cue location and/or 2) an increased ability to utilize spatial cues (see Figure 2.5) (Fan & Posner, 2004). In our data, the larger orienting effect in the PTSD group was driven by slower RT in center cue trials, indicating difficulty with disengaging attention from the central cue location and reorienting to the target location (Fan & Posner, 2004). Because the standard version of the ANT we used does not include invalid cues, we were unable to directly assess disengagement. Nonetheless, our findings are consistent with reports of disengagement impairments using the ANT in a cohort with mixed anxiety disorders (generalized, social, specific phobia, obsessive compulsive-disorder, agoraphobia and PTSD) (Pacheco-Unguetti et al., 2011) and in male veterans with PTSD and mTBI (Barlow-Ogden & Poynter, 2012). Problems with disengaging and shifting attention away from salient stimuli like threat or trauma cues may be a mechanism underlying PTSD symptom development (Aupperle et al., 2012). Our findings suggest that such problems are not specific to threatening stimuli. Rather, they may reflect a more general impairment of basic attentional processes that operate even on neutral stimuli. Alternatively, the deficits we have observed might comprise a predisposing risk factor for developing PTSD. Future longitudinal studies could be useful in making this distinction.

On the other hand, we found no evidence of increased utilization on spatial cue trials in PTSD. In fact, the PTSD group was nominally slower than controls to respond in spatial cue trials. These findings contrast with a previous report of increased utilization of spatial cues following an anxiety induction in healthy individuals (Garner, Attwood, Baldwin, & Munafò, 2012) and theoretical reports of facilitated orienting as a mechanism underlying attention biases (Weierich et al., 2008). Our findings suggest that these effects might be limited to healthy

individuals or relevant to threat stimuli only. Our results, however, are consistent with the neuropsychology literature describing PTSD deficits on the Trail-Making-Test-Part B (Hart et al., 2008; Jenkins et al., 2010; Koenen et al., 2001; Koso & Hansen, 2006; Lagarde et al., 2010; Madu & Peltzer, 2000; Polak et al., 2012; Stein et al., 2002; Sutker et al., 1995) and the Digit Symbol Test (Brandes et al., 2002; Hart et al., 2008; Jenkins et al., 2010; Parslow & Jorm, 2007). Successful completion of these tasks requires the participant to visually scan information and move his/her attention to a new spatial location.

We were unable to replicate the findings of Leskin and White, 2007 who reported that college students with PTSD had deficits with conflict monitoring, but not with orienting attention. Between-study differences (e.g., age, gender, population and symptom severity) could potentially account for the observed differences. Moreover, the smaller group size in their study could have reduced statistical power for detecting group differences in orienting attention. Clearly, additional research will be needed to clarify the influence of such factors on the nature of attentional deficits in PTSD.

Attentional performance and intrinsic network connectivity

There was a positive relationship between the orienting effect and cross-network connectivity in the control group. First there was a positive relationship between the orienting effect and salience network cross-network connectivity (dACC-default mode, dACC-dorsal attention, dACC-ventral attention). Second, there was a positive relationship between the orienting effect and dorsal attention network cross-network connectivity (middle frontal gyrus – salience network). Interestingly, larger orienting effects in the control group were driven by slower RT in center cue trials (same pattern as PTSD vs. control group finding), suggesting that

the cross-network connectivity effects above might reflect difficulty with disengaging attention from the center of the display. Consistent with this possibility, the SN and attention networks might be involved in DMN disengagement when salient stimuli are present (Daniels et al., 2010).

Another possibility is that cross-network connectivity leads to difficulties with reorienting, whereby SN intrusions upon other ICNs interfere with the DAN and VAN's ability to focus attention on the task at hand. The temporoparietal junction has been implicated in reorienting (Corbetta & Shulman, 2002), consistent with our findings that orienting effects were associated with greater dACC-left middle/superior temporal gyrus connectivity. Future studies will need to investigate whether SN cross-network connectivity on-task is related to difficulty with disengaging or reorienting attention.

Interestingly, we did not detect the same relationships between the orienting effect and cross-network connectivity in PTSD patients. First, we found no relationship between the orienting effect and dACC-DAN, dACC-VAN or MFG-SN connectivity. As this pattern was observed in the control group, normative relationships between intrinsic connectivity networks appear to be disrupted in PTSD. It is possible that attentional disengagement in PTSD is related to the connectivity of other neural structures in which we did not place seeds, such as the frontal eye fields and TPJ that are involved in shifting attention (Corbetta & Shulman, 2002). Future researchers might therefore employ a connectomics approach, rather than the present seed-based approach, to investigate ICNs.

We also found a negative relationship between the orienting effect and dACC-vmPFC connectivity, which was different from what we observed in the control group. In the control group, disengagement of attention was positively correlated with dACC-vmPFC connectivity.

One possible explanation for this seemingly discrepant finding, is that orienting to spatial cues, as well as disengagement from center cues, contributes to dACC-vmPFC connectivity in PTSD patients. When examining variability within the PTSD group, we found that greater intrusive symptoms were associated with slower RT on spatial cue trials and greater dACC-vmPFC connectivity.

Slower RT on spatial cue trials is reflective of a difficulty reorienting to the target location. This is an additional finding above and beyond the between group difference in disengagement that we observed. It is possible that difficulties with disengagement are a precursor to PTSD, or develop early on in the course of PTSD. Other factors such as mTBI or PTSD severity may then contribute to an additional deficit in the reorienting of spatial attention. Supporting this, we found that PTSD participants with mTBI exhibited slower RT to spatial cue trials compared those without mTBI. This is consistent with reports of orienting attention deficits following concussion (Pavlovskaya, Groswasser, Keren, Mordvinov, & Hochstein, 2007; van Donkelaar et al., 2005).

Greater connectivity between the dACC-vmPFC in the PTSD group could also reflect intrusive thoughts interfering with the ability of the SN to focus on spatial cues. The vmPFC is part of the DMN, that is thought to support stimulus-independent thought, such as day-dreaming and self-referential processing (Buckner & Vincent, 2007) and thus might be associated with intrusive thoughts as well. This could contribute to slower RT on spatial cue trials and the apparent "contradiction" whereby the orienting effect was larger in the PTSD group than controls, but negatively correlated with intrusive symptoms (see Figure 2.6). The seeming contradiction is simply the outcome of how the orienting effect is calculated – the difference in

RT between the spatial and the central cue trials. In both groups, increased connectivity between the SN and DMN may contribute to slower RTs – in controls by slowing mainly responses to central cues and in PTSD patients for whom disengagement is already affected, it may also slow responses to spatial cues.

We also replicated earlier findings (Brown et al., 2014; Lanius et al., 2010; Sripada, King, Welsh, et al., 2012; Zhang et al., 2015) of greater salience to default mode network (dACC-vmPFC) connectivity in PTSD. This was independent of ANT performance. We further extended this to show greater SN-DAN (right amygdala to right middle frontal gyrus) connectivity in PTSD independent of ANT performance. It is possible that SN intrusions upon the DAN may also contribute to difficulty orienting. Our findings were specific to the right amygdala, consistent with Barlow-Ogden et al. (2012) who found that orienting deficits in veterans with mTBI and PTSD were specific to the right hemisphere.

Together our findings support a notion that the normal relationship between intrinsic connectivity networks and orienting attention is disrupted in PTSD. Recent evidence points to ICN segregation as being important for normal cognitive development and functioning (Clare Kelly, Uddin, Biswal, Castellanos, & Milham, 2008; Mennes et al., 2010), suggesting that abnormal connectivity patterns might contribute to PTSD pathophysiology.

Limitations

Several limitations of the present study merit consideration. First, because we used community, rather than combat-exposed controls, it is possible that our findings are related to differences between military and non-military personnel. If our findings were due to military training, we would expect the PTSD group to show better performance than the controls, which

we did not observe, because heightened attention is heavily emphasized in military training (Messinger, 2013). Because IQ and general cognitive ability have been linked to attention performance (Schweizer & Moosebrugger, 2004) and cross-network connectivity (van den Heuvel, Stam, Kahn, & Hulshoff Pol, 2009), it is also possible our the findings are due to the differences in educational attainment between the two groups; however the findings held after controlling for level of education, which is correlated with IQ (Winship & Korenman, 1997). The findings could also be due to group differences in trauma exposure. Consistent with epidemiological studies (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995), 50% of our controls had experienced traumatic events and there were no significant differences in ANT performance between the subgroups, but future work with combat-exposed controls will be able to clarify whether our findings are partially related to trauma exposure. Second, the sample sizes of the control and PTSD groups were unequal; however, this was accounted for by statistical analyses that do not assume equal variance. Third, concerns have been raised regarding the psychometric properties of the ANT (Macleod et al., 2010). Past studies have found small interactions between the networks, however, we found them to be independent of one another ($p > 0.1$). Furthermore, in rsFC studies, it is difficult to determine the exact cognitive processes involved in the "rest" scan, which could contribute to group differences in rsFC. Lastly, all our participants were male and our sample size was moderate. Future studies will be needed to determine whether our findings extend to females.

Conclusion

Our results demonstrate that greater cross-network connectivity involving the SN is associated with impairments in the disengagement and orienting of attention, processes that were

altered in PTSD. These findings might suggest that both attentional orienting processes and the balance that is normally observed between the ICNs might be disrupted in veterans with PTSD. Interventions that utilize attention training, such as mindfulness (Shapiro, Carlson, Astin, & Freedman, 2006) might be useful for alleviating attentional impairments in PTSD. Further, our results suggest that interventions targeting orienting and disengagement deficits specifically may be a new avenue for PTSD research.

Chapter II Tables

Table 2.1.

Demographic and clinical characteristics of participants

Characteristic	PTSD (*N*=49)	Control (*N*=26)	t/χ^2	*p*
Age, M (SD)	31.49 (8.11)	31.00 (8.36)	0.246	0.806
Race, N (%)			7.979	0.092
White/European	45 (92)	20 (77)		
African American/Black	4 (8)	2 (7.7)		
Asian American	0	2 (7.7)		
Biracial	0	2 (7.7)		
Education, N (%)			10.958	0.004
Some graduate school or graduate degree	3 (6.1)	9 (34.6)		
Some college or college degree	36 (73.5)	15 (57.7)		
High school graduate	10 (20.4)	2 (7.7)		
CAPS, M (SD)	77 (17.81)	N/A	N/A	N/A
Comorbidities, N (%)		N/A	N/A	N/A
Depression	26 (53)			
Dysthymia	7 (14)			
Bipolar II	2 (4)			
Panic Disorder	4 (8)			
OCD	1 (2)			
Social Phobia	3 (6)			
Alcohol Abuse	4 (8)			
ADHD	1 (2)			
Medicated	38 (77.6)	N/A	N/A	N/A
mTBI	18 (36.7)	N/A	N/A	N/A

Note. ADHD, Attention-Deficit-Hyperactivity Disorder; mTBI, mild-moderate traumatic brain injury; OCD, Obsessive-Compulsive Disorder; PTSD, posttraumatic-stress disorder. Those with mTBI (*M*=83.33) had greater CAPS scores than those without mTBI (*M*=73.57) at a trend level, $t(46) = 1.838$, $p = 0.072$. There were no significant differences on any ANT measures between those who were on medications and those who were not. No participants met criteria for serious mental illness such as psychosis, substance dependence or mania. Removal of those with alcohol abuse, bipolar II and ADHD did not affect the results.

Table 2.2.
Regions of interest for connectivity analyses

ICN	Seed (x,y,z coordinates)	Search Mask (x,y,z coordinates)
SN	dACC, (-4,6,40)	1) dACC (+/-4,6,40) Insula/Precentral gyrus (+/- 51, -7,8) 2) Bilateral anatomical amygdala
VAN	IFG (52,26,-4)	IFG (+/-52,26,-4) Middle temporal gyrus, (+/-62,-37,-3)
DAN	MFG, (46,6,34)	MFG (+/-46,6,34) Inferior parietal lobule (44,-48,46) Superior parietal lobule (-38,-56,48)
DMN	N/A	PCC (+/-2,-51,27) vmPFC (+/-2,54,-3) Hippocampus (+/-20,-19,-18)

Note. dACC, dorsal anterior cingulate cortex; DAN, dorsal attention network; DMN, default mode network; ICN, intrinsic connectivity network; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; PCC, posterior cingulate cortex; SN, salience network; VAN, ventral attention network; vmPFC, ventromedial prefrontal cortex. 10-mm-spheres were created around each coordinate based on (De Luca et al., 2006). The anatomical amygdala (k = 264) was defined by the WFU Pick Atlas (Maldjian, Laurienti, & Burdette, 2004; Maldjian, Laurienti, Kraft, & Burdette, 2003; Tzourio-Mazoyer et al., 2002) and included because it has been described as part of the salience network (Seeley et al., 2007) and was implicated in previous PTSD rsFC studies (Rabinak et al., 2011; Sripada, King, Garfinkel, et al., 2012; Sripada, King, Welsh, et al., 2012), but did not appear in the previous rsFC study from which the other SN ROIs were chosen (De Luca et al., 2006).

Table 2.3.
Reaction time on the ANT in the PTSD and control group

ANT Component	PTSD M (ms), SD	Control M (ms), SD	Main effect trial type F, *p*	Main effect group F, *p*	Interaction F, *p*
Alerting			8.32, *0.005*	5.10, *0.023*	0.85, *0.36*
No cue	671.38, 118.63	599.09, 98.57			
Double cue	629.67, 117.31	564.31, 93.28			
Orienting			20.38, *<0.001*	4.66, *0.034*	6.31, *0.014*
Center cue	650.64, 128.27	574.32, 105.24			
Spatial cue	598.13, 126.50	537.41, 92.57			
Conflict			29.88, *< 0.001*	5.18, *0.026*	2.02, *0.16*
Congruent	598.88, 123.04	536.02, 89.19			
Incongruent	723.68, 135.18	643.10, 116.19			

Note. ANT, Attention Network Task.

Table 2.4.
A*ccuracy on the ANT in the PTSD and control Group*

	PTSD M (%), SD	Control M (%), SD	*F*	*P*
All trial types	96.53, 6.57	98.18, 1.88	0.926	0.34
No cue	96.49, 6.24	98.24, 1.98	1.114	0.30
Double cue	96.15, 6.89	98.18, 1.96	1.267	0.26
Center cue	96.46, 7.13	97.92, 2.84	0.641	0.43
Spatial cue	97.14, 6.49	98.45, 2.09	0.627	0.43
Incongruent	95.20, 10.40	97.14, 3.01	0.628	0.43
Congruent	99.14, 1.81	99.60, 0.56	0.634	0.43

Note. ANT, attention network task; PTSD, posttraumatic-stress disorder.

Table 2.5.
Correlation of DAN (MFG seed) connectivity with the orienting effect

Contrast Map and Brain Region	Cluster Size	MNI Coordinates (x y z)	Analysis (z)	*p* (SVC)
All Participants		No significant clusters		
PTSD		No significant clusters		
Control				
Right Amygdala	9	18 -1 -14	3.40	0.032
PTSD>Control		No significant clusters		
Control>PTSD				
Right Amygdala	14	18 -1 -14	3.38	0.047

Note. MNI, Montreal Neurological Institute; PTSD, posttraumatic-stress disorder; SVC, small volume correction. All correlations are positive.

Table 2.6.
Correlation of SN (dACC seed) connectivity with the orienting effect

Contrast Map and Brain Region	Cluster Size	MNI Coordinates (x y z)	Analysis (z)	*p*-value (FWE, FDR)
All Participants				
VAN				
L Mid/Sup Temporal gyrus	46	-60 -34 1	3.06	0.317, 0.324 (0.041 SVC with VAN mask)
PTSD				
DMN				0.620, 0.599
vmPFC*	28	21 50 -2	3.30	(0.025 SVC with DMN mask)
Control				
DMN				
vmPFC	362	9 38 -11	3.93	<0.001,
Precuneus	361	-15 -46 4	3.70	<0.001
L Parahippocampal gyrus/hippocampus	124	-27 -19 -23	4.21	< 0.001, <0.001
R Parahippocampal gyrus/hippocampus	203	33 -7 -38	4.09	0.118, 0.035
				0.014, 0.005
DMN/DAN				
L angular gyrus	359	-27 -79 58	4.10	
R angular gyrus	106	51 -64 34	3.59	
				<0.001,
VAN				<0.001
L Sup temporal gyrus				0.199, 0.048
R Mid/Inf/Sup temporal gyrus	112	-27 11 -47	4.34	
	528	60 -10 -29	4.45	
R Inf frontal gyrus	136	42 20 -35	3.65	0.167, 0.045
				< 0.001, <0.001
				0.084, 0.048
PTSD>Controls		No significant clusters		
Controls>PTSD				
DMN				
vmPFC	342	12 47 1	4.17	0.002, 0.005
PCC	118	-12 -34 28	3.62	0.242, 0.086
DAN				
L Sup frontal gyrus	216	-33 2 70	3.81	0.027, 0.014
R Sup frontal gyrus	232	24 29 55	3.97	0.019, 0.014

VAN				
L Sup temporal gyrus	182	-33 20 -38	3.72	0.057, 0.025
R Mid/Inf temporal gyrus	241	60 -16 -41	3.81	0.027, 0.015

Note. DAN, dorsal attention network; FDR, false discovery rate; FWE, family-wise error; Inf, inferior; L, left; Mid, middle; MNI, Montreal Neurological Institute; PCC, posterior cingulate cortex; R, right; SN, salience network; Sup; superior; VAN, ventral attention network; vmPFC, ventromedial prefrontal cortex.
*Negative correlation in PTSD group between orienting effect and dACC-vmPFC connectivity. All other correlations in the table are positive.

Chapter II Figures

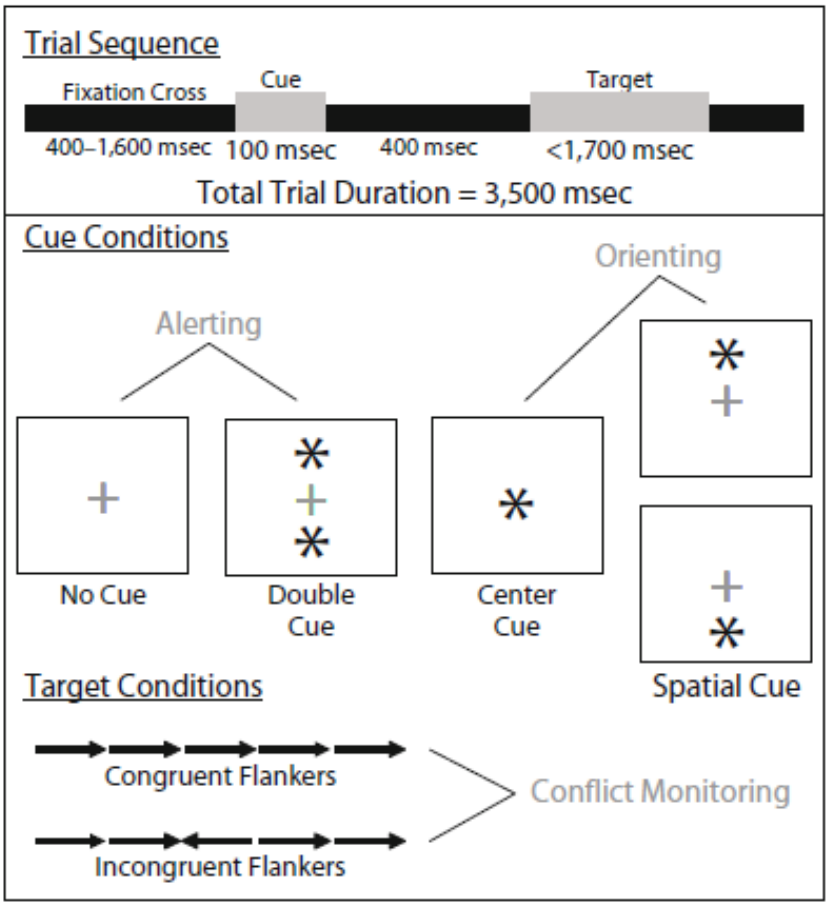


Figure 2.1. Schematic of the Attention Network Task (ANT) adapted from Jha, Krompinger, & Baime, 2007.

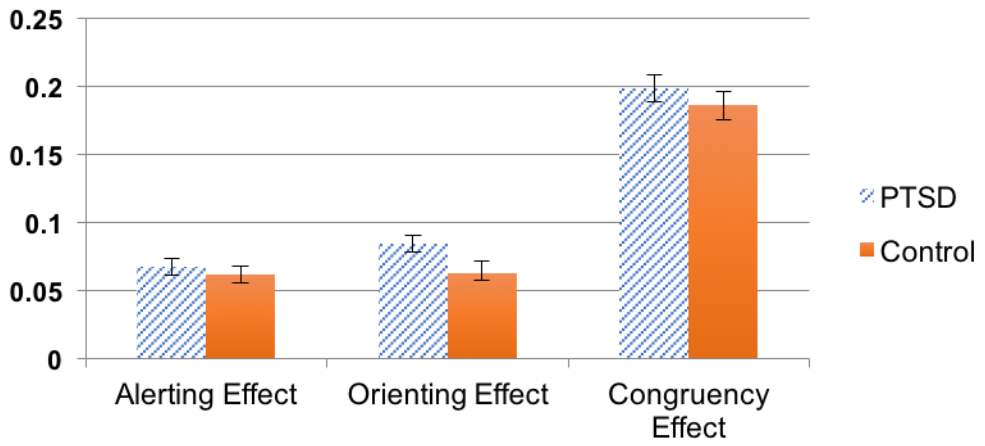


Figure 2.2. Group differences in reaction time on the Attention Network Task.
The PTSD group exhibited a larger orienting effect compared to controls, (p = 0.014 for raw RT, p = 0.030 when controlling for mean RT), but no difference in the magnitude of the alerting or conflict effects. Results plotted above display the mean for each ANT component normalized by dividing the effect by the mean RT on the task as a whole +/- standard error of the mean.

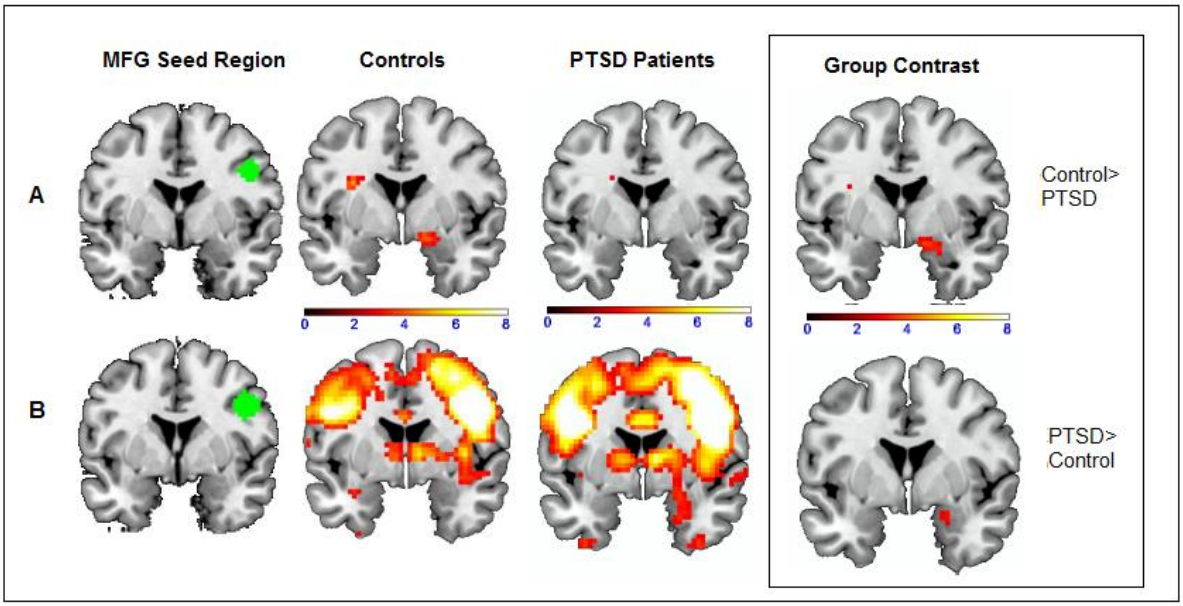


Figure 2.3. Functional connectivity analysis of the dorsal attention network.
A) Correlation of DAN connectivity with the orienting effect. The orienting effect increased with cross-network functional connectivity between the DAN (right MFG seed) and the SN (right amygdala) in the control group, but there was no such relationship in the PTSD group.
B) Functional connectivity of the MFG seed without ANT regressors. PTSD patients showed greater connectivity between the MFG seed and the right amygdala than the controls.
Slices displayed at Montreal Neurological Institute coordinates $y = -1$ (top row) and $y = 1$ (bottom row). Results are corrected for multiple comparisons within ROIs.

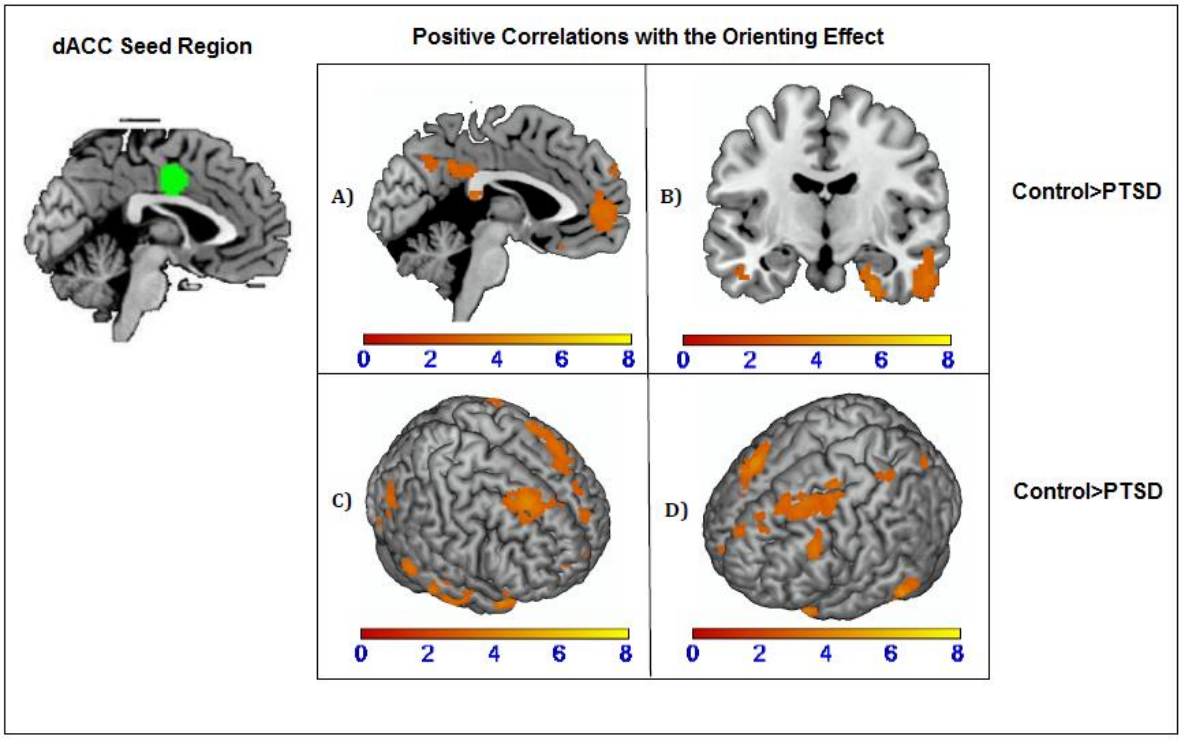
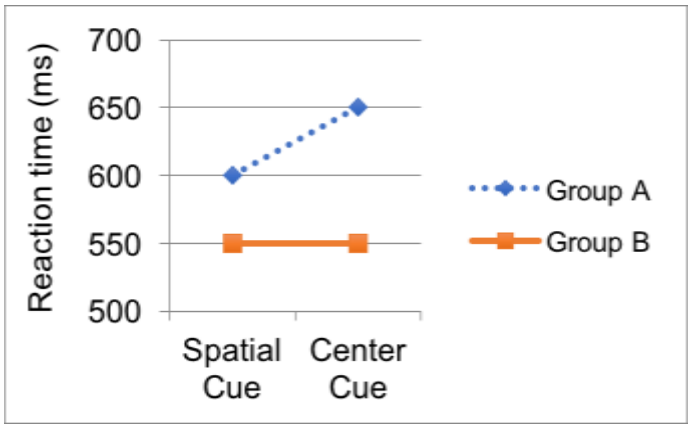


Figure 2.4. Interaction of salience network connectivity x the orienting effect x group status. Controls showed greater connectivity correlated with the orienting effect than PTSD patients between the dACC seed and several regions of the DMN including (A) the PCC and vmPFC and (B) the right hippocampus, as well as the DAN (C, D) in the bilateral superior frontal gyrus and several regions of the VAN (B, C, D) including the middle and superior temporal gyrus.
Images (A) and (B) are displayed at Montreal Neurological Institute coordinates x = -3 and y = -10, respectfully, while (C) and (D) are whole brain connectivity displayed at azimuth 120°, elevation 45° and azimuth 240°, elevation 45° respectively. Results are corrected for multiple comparisons within ROIs using FWE $p < .05$ at the cluster level.

A



B

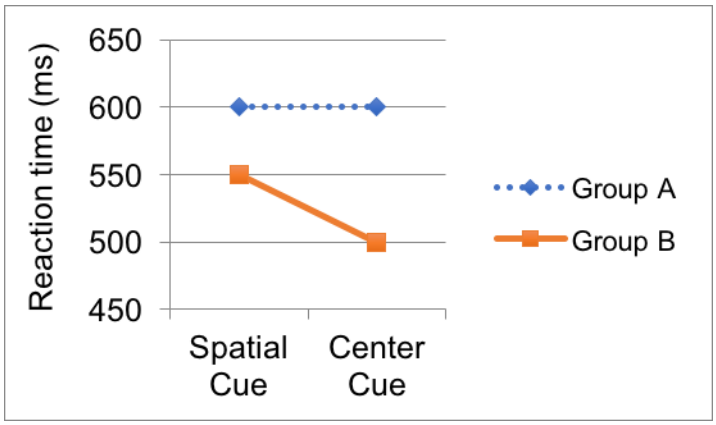


Figure 2.5. Hypothetical data showing how a group difference in the orienting effect could be driven by A) disengagement or B) spatial orienting.
In our data, the PTSD group had a larger orienting effect than the control group, driven by slower RT to center cue trials, consistent with graph A.

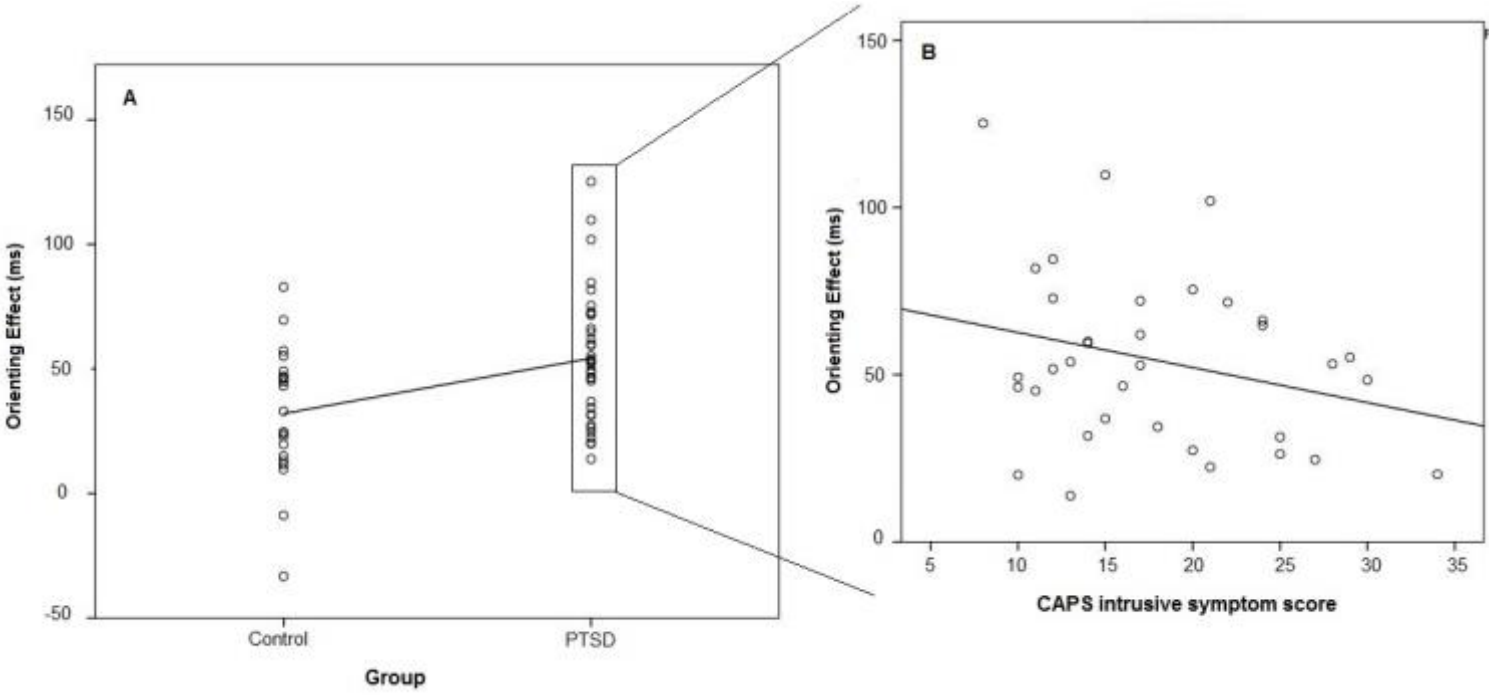


Figure 2.6. The magnitude of orienting effect between and within groups.
A) The PTSD group displayed a larger average orienting effect than the control group. B) Within the PTSD group, however, greater intrusive symptoms were associate with smaller orienting effects.

CHAPTER III

Experiment 2: Resting-state functional connectivity predicts neural functioning on the ANT

Experiment 1 demonstrated that resting-state functional connectivity (rsFC) is predictive of performance on the attention network task (ANT) in healthy individuals. We found that in healthy controls, greater salience network (SN) cross-network connectivity was associated with larger ANT orienting effects. One limitation of Experiment 1 was that the ANT was performed outside of the scanner. Therefore, we were unable to determine the link between brain functioning during an attention task and ICN functioning during rest. Understanding this relationship is an important first step in understanding the significance of resting-state alterations in psychiatric populations such as PTSD.

There is evidence to support the view that rsFC is related to task-induced brain function. Brain regions that comprise intrinsic connectivity networks (ICNs) are noted to activate together (Smith et al., 2009) and show coherent connectivity during active tasks (Hampson et al., 2006; Harrison et al., 2005). Furthermore, several studies have reported that rsFC is predictive of task-related behavior (Madhyastha, Askren, Boord, & Grabowski, 2015; Stevens, Tappon, Garg, & Fair, 2012; Visintin et al., 2015), activity (Mennes et al., 2010) and connectivity (Cocchi, Zalesky, Fornito, & Mattingley, 2013). For example, greater rsFC within attention networks and decreased rsFC between attention networks and the default-mode network (DMN) was predictive of greater activation of attention regions in a flanker task (Mennes et al., 2010). However, there

have been no studies linking functional connectivity in attention-related ICNs at rest to activity on the ANT

Recent attention research has demonstrated that orienting attention can be divided into separate subcomponents, each involving separate brain regions: disengagement, moving and engagement (Fan et al., 2009). During the orienting process, one must first disengage attention from the current stimulus or modality, then move attention to the new stimulus or modality and finally, engage attention to the new stimulus or modality. Disengaging and reorienting attention in trials with invalid cues activates both the ventral attention network (VAN) and the dorsal attention networks (DAN). In contrast, moving, engaging and orienting attention in trials with valid cues activates the SN and the DAN (Petersen & Posner, 2012). Because the group differences in orienting attention that we observed in Experiment 1 were driven by different reaction times (RTs) in central (not spatial) cue trials, we hypothesized that they reflect group differences in disengaging attention. Therefore, in Experiment 2, we used a modified ANT to investigate this possibility. In this modified version, the comparison of valid spatial cue trials to neutral center cue trials measures moving and engaging, while the comparison of invalid spatial cue trials to neutral center cue trials measures disengagement. The entire orienting process from the cost of disengaging from an invalid location to the benefit of receiving valid spatial information can be measured by comparing invalid to valid cue trials, which is called the validity effect. The validity effect is not a separate attention component of Posner's model. Instead it reflects multiple subprocesses involved in orienting and is therefore a useful way to compare performance in each.

Hypotheses

The aim of Experiment 2 was to examine the associations between rsFC in attention-related ICNs, behavioral performance, neural activation and on-task connectivity during an attention task (ANT). For this experiment, we used a combined sample of healthy subjects, trauma-exposed and non-trauma-exposed controls in order to improve the power to observe relationships between rest and task measures. We then examined these relationships in the non-trauma exposed group alone. In the following chapter, we will examine group differences in these measures. For Experiment 2, we investigated three main hypotheses.

2.1) During performance of the ANT, the alerting effect (no cue – center cue) will be associated with activity in the VAN and SN, the validity (invalid cue – valid cue) and disengagement effects (invalid cue – center cue) will be associated with activity in the VAN and the DAN, the orienting effect (center cue – valid cue) will be associated with activity in the DAN and the conflict effect will be associated with activity in the SN and FPCN.

2.2) Coherence of attentions ICNs at rest will predict greater activation and connectivity of attention regions during the ANT.

2.3) Greater SN cross-network connectivity at rest will be associated with difficulties in orienting and disengagement.

Methods

Participants. We recruited 63 individuals in three groups: PTSD (*N*=24), trauma-exposed controls (TEC; *N*=20) and non-trauma exposed controls (NTC; *N*=19). Participants were recruited from the Ann Arbor community via the UM health system research registries and flyers. Control participants were matched to participants in the PTSD group based on age,

gender and race (see Table 3.1). *Inclusion Criteria:* All Groups: normal or corrected-to-normal vision and ability to consent to the protocol. PTSD group: current PTSD diagnosis or current PTSD symptoms (at least four out of seven diagnostic criteria). TEC group: history of a traumatic event meeting DSM criterion A, no current psychiatric disorder and no lifetime history of PTSD. NTC group: No lifetime history of a traumatic event or psychiatric disorder. *Exclusion Criteria:* a) significant medical or neurologic condition (i.e. stroke, seizure disorder, multiple sclerosis); b) currently pregnant; c) left-handed; d) contraindication for fMRI; e) life history of psychosis, organic mental syndrome, mental retardation, or pervasive developmental disorder; f) active suicidal ideation with plan or intent; g) alcohol/drug abuse or dependence in the past 6 months; h) Axis II personality disorder; or i) unwilling or unable to sign informed consent document. Participants on psychiatric medications were required to be on a stable dosage for at least four weeks prior to the MRI scan. One person in the NTC group and two people in the PTSD group were lost-to-follow up. Additionally, one person in the PTSD group did not complete the MRI portion of the study due to claustrophobia.

The study was approved by the Institutional Review Boards at the University of Michigan and the Ann Arbor VA. We obtained written informed consent after providing a complete description of the study to participants.

Measures.

***Psychiatric History*.** Lifetime history of traumatic events and PTSD diagnosis was determined by the Life Events Checklist and the Clinician Administered PTSD Scale (CAPS) for the DSM-V, (Weathers et al., 2017), while history of other psychiatric disorders was determined by the Mini-International-Psychiatric Interview (MINI), a structured clinical interview that

assesses DSM-IV disorders (Sheehan et al., 1998). Lifetime history of head injury was assessed by self-report. Individuals were classified as having a mild traumatic brain injury (mTBI) if they lost consciousness or had two or more post-concussive symptoms, per the Center for Disease Control (Centers for Disease Control and Prevention, 2013). Participants also completed a series of self-report measures, which will be analyzed and reported elsewhere. These included the Connor's Adult ADHD Rating Scale, the Cognitive Emotion Regulation Questionnaire, the Rumination Questionnaire, the Beck Depression Inventory II and the State-Trait Anxiety Questionnaire).

Resting-state fMRI task. Participants completed the same resting-state paradigm as in Experiment 1.

Modified Attention Network Test. We modified the original version of the task (described in Experiment 1) to be suitable for the fMRI environment and to include disengagement trials (see Figure 3.1). We based our modifications on two prior ANT studies (Fan et al., 2009, 2005). In this event-related task, a white central fixation dot subtending 0.5° of the visual angle is presented in the center of a black screen throughout the entire task. In each trial, one of two cue types, subtending 0.75° of the visual angle, is presented for 100 ms (center cue or spatial cue trials) or the screen remains unchanged (no cue condition). The center cue is a white circle that surrounds the central fixation dot, while the spatial cue is a white circle which appears 2° to the left or right of the central fixation dot. The former provides temporal information about the onset of the upcoming target, while the latter provides temporal and spatial information. Spatial cues are valid when the target appears in the same location as the cue, but invalid when they appear in the opposite location of the target. On target trials, a column of five

arrows appears 2° to the left or right of the central fixation dot 200 ms after the cue, while on cue only trials, no arrows appear. The interval between the cue and the target is designed to minimize inhibition of return (Klein, 2000). The participant's task is to identify the direction of the central target arrow by pressing the thumb of the right hand to indicate "down" or the pointer finger of the right hand to indicate "up." The central arrow is flanked by four arrows (two above and below) that either all point in the same direction as the central arrow (congruent trials) or in the opposite direction (incongruent trials). The arrows are presented for 300 ms followed by a 1350 ms response window. At the end of every trial, the central fixation dot turns red for 150 ms to signal the end of the trial. The purpose of the end of trial signal is to inform participants that they can stop attending for the target arrow on cue only trials, thus preventing confusion with cue information presented in the subsequent trial (Corbetta et al., 2000). The duration between the end of trial signal and the onset of the following trial is jittered with a mean duration of 3250 ms and a standard deviation of 1500 ms.

The task consists of four runs of 65 trials each for a total of 260 trials across the task. The 260 trials are divided amongst cue conditions as follows: 32 no cue trials, 32 center cued target trials, 128 valid cue trials and 32 invalid cue trials, yielding an 80% valid contingency. Additionally, there are 36 cue only trials (12 center, 12 spatial right, 12 spatial left) that are not followed by targets, in order to better separate the brain activity of cues and targets (Ollinger, Shulman, & Corbetta, 2001; Weissman, 2004). For the target conditions, there are 112 congruent trials and 112 incongruent trials that follow each cue type equally as often to prevent cue-related effects from being confounded with expectations about upcoming trial conflict. Additionally, the spatial cues and targets are presented equally as often on the left and right side

of the screen. Each run lasts approximately six minutes for a total completion time of approximately 24 minutes.

Procedure. The study took place over the course of two study visits. At the first study visit, participants completed a self-report measures and a diagnostic interview to determine eligibility, which was conducted by either a doctoral level psychology student or a registered nurse, both trained in the administration of the measures.

At the second study visit, participants underwent structural and functional MRI scanning. The second study visit occurred an average of 7.17 days following the first study visit (*SD* = 5.88). The functional MRI scan included a resting-state task, the ANT and the shifted emotional appraisal task, which will be analyzed and reported elsewhere. The resting-state task always occurred before the attention and emotional regulation tasks.

FMRI data acquisition. FMRI data was acquired following the same parameters as Experiment 1.

Data analyses. To increase power, all analyses were conducted first in all participants, followed by the NTC group alone. Experiment 3 will analyze group differences.

ANT behavioral analysis. Within-participants *t*-tests were used to test for the effects of cue/flanker type on the five ANT effects (Fan et al., 2009). For each comparison, only the mean RT for correct trials was used (Xuan et al., 2016). Incorrect responses and omissions were excluded from the ANT effect calculations. Runs in which a subject's accuracy was less than 75% were excluded (one PTSD subject – all runs, three PTSD participants – three runs, one PTSD subject – two runs, one PTSD subject - one run, two TEC subject – two runs, two NTC participants - two runs). RT outliers, defined as responses made after the designated response

window (Xuan et al., 2016), were excluded if they were more than two standard deviations greater than the mean RT for the individual subject (seven trials from four PTSD participants, three trials from three TEC participants and two trials from two NTC participants). There were no lower boundary RT outliers defined as responses that were less than 200 ms (Fan et al., 2007; Gamboz, Zamarian, & Cavallero, 2010). The alerting effect was then defined as the mean RT on center cue trials subtracted from the mean RT on no cue trials. The orienting effect (moving and engaging) was defined as the mean RT on valid spatial cue trials subtracted from the mean RT on central cue trials. The disengagement effect was defined as the mean RT on invalid cue trials subtracted from the mean RT on center cue trials. The validity effect was defined as the mean RT on invalid cue trials subtracted from the mean RT on valid cue trials. Finally, the conflict effect is defined as the mean RT on congruent flanker trials subtracted from the mean RT on incongruent flanker trials.

ANT neural activation analysis. Functional data was processed and analyzed using conventional methods (GLM, event-related design and random effects) with Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology, London). Runs in which participants had greater than 3 mm of head movement were excluded. To examine the significant BOLD signal differences in each ANT condition, a generalized linear model was conducted with 11 task-related regressors and 6 motion regressors of non-interest. The 11 task-related regressors included two for the cue presentation period (center cue and spatial cue), eight for the target presentation and response period (congruent and incongruent trials preceded by no cue, center cue, valid cue and invalid cue) and one for omissions and outlier RT trials which were modeled over the entire trial period (cue and target time). Because 80% of the commission

errors occurred on incongruent trials, commission trials were included in the main ANT contrasts to prevent losing variance in the conflict condition.

Five contrasts were then defined for each of ANT effect of interest. The *Alerting contrast* was defined as the linear contrast of center cue compared to baseline. The *Orienting contrast* was defined as the linear contrast of spatial cue compared to center cue. The *Disengagement* contrast was defined as the linear contrast of invalidly cued targets compared to validly cued targets. The *Validity contrast* was defined as the linear contrast of validly cued targets compared to center cued targets. Lastly, the *Conflict contrast* was defined as the linear contrast of incongruent targets compared to congruent targets.

In addition to the specific ANT contrasts, we also examined activity during all trials. All cue processing was defined as the average of center cues plus spatial cues weighted by 1/3 as they occurred three times as often as center cues. All target processing was defined as the average of eight target presentation regressors with spatially cued targets weighted as ¼ as they occurred four times as often as other targets. Findings are presented at the whole brain level using a family-wise-error threshold of $p < 0.05$ for multiple comparisons and a voxelwise threshold of $p < 0.005$ uncorrected.

ANT on-task connectivity. To evaluate the functional connectivity during attentional processes, we utilized a psychophysiological interaction (PPI) analysis. Activation peaks from the five ANT contrasts across all participants were chosen as seeds. Based on *a priori* hypotheses (Vossel et al., 2014; Xuan et al., 2016), we selected peaks that overlapped with the resting-state ICNs in our data. Specifically, we selected the right inferior frontal gyrus (IFG) [33, 29, 1] and brainstem [6 -31 -8] for seeds in the *Alerting contrast* (overlapped with VAN at

rest), the right superior parietal lobule (SPL) [24, -58, 58] and right middle frontal gyrus (MFG) [30, -1, 49] for seeds in the *Orienting contrast* (overlapped with DAN at rest), supplementary motor area (SMA) [9, 14, 64] as the seed for the *Conflict contrast* (overlapped with SN at rest), the right IFG [33, 26, -2] and right MFG [36, 5, 43] as seeds for the *Validity contrasts* (overlapped with VAN and DAN at rest) and the right temporoparietal junction (TPJ) [48, -34, 1] and right IFG [48, 23, -5] as seeds for the *Disengagement contrast* (overlapped with VAN at rest). For each coordinate, we created a sphere with a 5-mm radius to define the seed. Deconvolved time series from these seeds for each participant was multiplied by a vector representing each contrast of interest (center cue>baseline; valid spatial cue>center cue; incongruent flanker>congruent flanker; validly cued targets> invalidly cued targets; center cued targets>invalidly cued targets) and individual models containing regressors for the seed time series, the original conditions and the interaction terms were convolved with the canonical hemodynamic response function. Resulting contrast maps were entered into second-level random effects analyses to determine functional connectivity of each seed across all participants, followed by the NTC group alone. Findings were small volume corrected within a search mask of all task positive activation (cues and targets in all participants at a threshold of $p < 0.001$ uncorrected), using a family-wise error correction at the cluster level with a voxelwise threshold of $p < 0.005$ uncorrected.

Resting-state fMRI analysis. Resting-state data was processed and analyzed using the same methods as Experiment 1. Seeds in the IFG, MFG, dorsal anterior cingulate cortex (dACC) and posterior cingulate cortex (PCC) from Experiment 1 were used to probe connectivity of the VAN, DAN, SN and DMN, respectively. Findings were small volume corrected using the same

ICN search masks as in Experiment 1 using a family-wise error correction at the cluster level with a voxelwise threshold of $p < 0.005$ uncorrected.

We then conducted three sets of analyses to determine the relationship between resting-state functional connectivity and task behavioral performance, neural activity and connectivity on the ANT (see Figures 3.12-3.16). 1) To test link between behavioral performance and rsFC - First, we entered the alerting, orienting, validity, disengagement and conflict RT effects of the ANT as regressors in the resting-state analyses to determine the correlation of the behavioral attention components with the VAN, DAN and SN, respectively. We examined the correlation of IFG seed connectivity with the alerting effect, MFG connectivity with the orienting effect, both IFG and MFG seed connectivity with the validity and disengagement effects and dACC seed connectivity with the conflict effect. We also examined the correlation of dACC seed connectivity with the orienting effect to see if we would replicate our findings from Experiment 1. Findings are presented at the whole brain level using a family-wise-error threshold of $p < 0.05$ for multiple comparisons and a voxelwise threshold of $p < 0.005$ uncorrected. Significant brain-behavior correlations were extracted to determine directionality by examining the correlation with individual trials types correcting for mean RT.

2) To test link between neural activity on the ANT and rsFC - Second, we examined if resting-state functional connectivity would predict task activity by extracting the connectivity of each resting-state seed with its corresponding ICN nodes based on the mask in Experiment 1 (right IFG connectivity with left IFG, right and left middle temporal gyrus (MTG); right MFG connectivity with left MFG, right SPL, interior parietal lobule (IPL); dACC connectivity with bilateral insula and amygdala). We then entered each network's connectivity simultaneously as

regressors into the corresponding ANT activation contrast as follows: IFG seed regressors in the *Alerting contrasts*, MFG seed regressors in the *Orienting contrasts*, both IFG and MFG seed regressors in the *Validity* and *Disengagement contrasts* and dACC seed regressors in the *Conflict contrast* in order to determine the correspondence of VAN, DAN and SN task-related activation with VAN, DAN and SN resting-state connectivity. Findings were corrected for multiple comparisons using a family-wise error correction of a $p < 0.05$ across the entire brain with a voxelwise threshold of $p < 0.005$ uncorrected.

3) To test link between neural connectivity during the ANT and rsFC - Third, we examined if resting-state functional connectivity would predict on-task connectivity. To this end, we entered each resting state network's connectivity simultaneously as regressors into the corresponding ANT PPI contrast as follows: IFG seed regressors in the *Alerting contrast* (IFG and brainstem PPI seeds), MFG seed regressors in the *Orienting contrast* (right SPL and MFG PPI seeds), both IFG and MFG seed regressors in the *Validity contrast* (IFG and MFG PPI seeds). We did not examine the relationship of rsFC with connectivity in the *Disengagement* or *Conflict contrast* as there were no significant connectivity was observed for these contrasts (see Table 3.4). Findings were corrected for multiple comparisons using a family-wise error correction of a $p < 0.05$ across the entire brain with a voxelwise threshold of $p < 0.005$ uncorrected.

Results

ANT behavior.

Within participants t-test revealed significant effects for each of the five ANT components (see Figure 3.2): Alerting, $t(58) = 11.97$, $p < 2.2e\text{-}16$; Orienting, $t(58) = 10.48$, $p =$

5.4e-15; Conflict, $t(58) = -11.071$, $p = 6.26e-16$; Validity, $t(58) = -14.65$, $p < 2.2e-16$; and disengagement $t(58) = -4.012$, $p = 0.0002$. These effects were also significant in the NTC group alone: Alerting, $t(18) = 8.90$, $p = 5.213e-08$; Orienting, $t(18) = 9.9228$, $p = 1.006e-08$; Conflict, $t(18) = -5.6837$, $p = 2.168e-05$; Validity, $t(18) = -10.692$, $p = 3.157e-09$; and disengagement $t(18) = -4.133$, $p = 0.0006$. The overall accuracy on the task was 95.65%. There were more commission errors on incongruent trials (80.7% of trials) than would be expected by chance (50%), $\chi^2(1) = 18.2$, $p < 0.001$. There were more commission errors made on invalid cue trials (22% of trials) than would be expected by chance (14.2%), $\chi^2(1) = 4.28$, $p < 0.05$. For trials in which participants omitted a response, there were a greater proportion in the center cue condition (20%) than would be expected by chance (14.2%), $\chi^2(1) = 6.76$, $p < 0.01$, but a smaller proportion in the invalid cue condition (0.05%), $\chi^2(1) = 13.22$, $p < 0.001$. There were no differences in omission rates for congruent and incongruent trials.

ANT task activation.

In all participants, the ANT activated expected areas for each of the five contrasts (see Table 3.2, Figure 3.3). Activation during the cue processing period (*Alerting* and *Orienting contrasts*) was stronger than those in the target processing period (*Conflict, Validity* and *Disengagement contrasts*). The *Alerting contrast* showed activation in the bilateral superior temporal gyrus and right IFG consistent with the VAN and as well as the bilateral MFG, occipital lobe, supplementary motor area (SMA), dACC, brainstem, putamen and parahippocampus. The *Orienting contrast* showed activation in bilateral MFG and superior parietal regions consistent with the DAN, as well as the bilateral occipital lobe, SMA. The *Conflict contrast* showed activation in the SMA, but this was only significant at an uncorrected

threshold. The *Validity* and *Disengagement contrasts* showed activation in both VAN and DAN regions as expected including the IFG, MFG and right TPJ, however, only a cluster in the right temporal and occipital gyrus reached whole brain significance in the *Validity contrast* (there were not whole brain significant findings in the disengagement contrast).

In the NTC group only, the similar activations were observed on the ANT as in all participants (See Table 3.3). For the *Alerting, Orienting* and *Validity contrasts*, peaks in the same regions were observed, but with a decrease in statistical significance. For the *Disengagement contrast*, a larger peak was observed in the TPJ ($k = 43$, $p = 0.608$ FWE) than in the contrast of all participants ($k = 6$, $p = 1.00$ FWE), possibly reflecting disengagement difficulties in trauma-exposed populations, consistent with Experiment 1. Finally, for the *Conflict contrast*, there were no significant clusters.

ANT task connectivity.

In all participants, significant on-task functional connectivity was only observed for the *Alerting contrast* (see Table 3.4; Figure 3.4). During alerting, connectivity was observed between the IFG seed and a) the pons extending to the cerebellum and culmen and b) the bilateral middle occipital gyrus. There was also connectivity between the IFG seed and a) the right insula and b) the right middle temporal gyrus, but these did not survive correction for multiple comparisons. Additionally, during *Alerting*, connectivity was observed between the brainstem seed and multiple task-positive regions including the insula, putamen, cerebellum, IPL, parahippocampus, brainstem and occipital lobe. In the NTC group alone, similar connectivity was observed but with decreased statistical significance (see Table 3.5).

For the *Orienting* and *Validity contrasts*, connectivity was observed with several task-positive regions, but these peaks did not survive correction for multiple comparisons. Interestingly, during orienting, both seeds exhibited positive connectivity with the parahippocampus, while during validity, positive connectivity was observed the MFG seed and the hippocampus. Connectivity was also observed between the seeds and a) cerebellum, b) visual processing areas and c) the middle temporal gyrus, but these were only significant at an uncorrected *p* value at the voxelwise level.

There was no connectivity observed during the *Conflict* or *Disengagement contrasts*.

Resting-state functional connectivity.

Expected ICNs present at rest. In all participants and the NTC group alone, the expected functional connectivity was observed within ICNs for each *a priori* chosen seed (see Table 3.6, Table 3.7, Figure 3.5). The right IFG seed exhibited significant positive functional connectivity with the left IFG and bilateral MTG, consistent with the VAN. The right MFG seed exhibited significant positive functional connectivity with the left MFG and the bilateral inferior/superior parietal lobe, consistent with the DAN. The dACC seed exhibited significant positive functional connectivity with the bilateral insula and amygdalae, consistent with the SN. Lastly, the PCC seed exhibited significant positive functional connectivity with the ventromedial prefrontal cortex (vmPFC) and bilateral hippocampi.

1) Correlation of resting-state functional connectivity with ANT performance. Four resting-state connectivity relationships significantly predicted behavior in all participants (see Table 3.8, Figure 3.6). First, greater right IFG- right middle/inferior temporal gyrus connectivity was associated with larger alerting scores. Post-hoc tests controlling for mean RT showed that

greater connectivity between these regions was associated with slower RT in no cue trials, $r(51) = 0.29$, $p = 0.03$, but faster RT in center cue trials, $r(51) = -0.30$, $p = 0.03$. Second, right IFG – right insula connectivity was negatively correlated with validity scores, driven by slower RT in valid cue trials, $r(51) = 0.41$, $p = 0.002$ and faster RT in invalid cue trials, $r(51) = -0.28$, $p = 0.04$ after controlling for mean RT. Third, right MFG- right superior medial frontal gyrus connectivity negatively correlated with disengagement, driven by slower RT in center cue trials, $r(51) = 0.26$, $p = 0.06$. It was also associated with slower RT in invalid cue trials, but was not significant, $p = 0.11$. Fourth, connectivity of the dACC with the right IPL and supramarginal gyrus predicted smaller conflict scores. Post-hoc test revealed that greater connectivity was associated with faster RT in both incongruent trials ($r = -0.43$, $p = 0.001$) and congruent trials ($r = -0.31$, $p = 0.02$). In summary, while some rsFC connections were predictive of behavior, rsFC within ICNs was largely not informative about ANT performance.

Additionally, we partially replicated our findings from Experiment 1 regarding SN-DMN connectivity correlations with the orienting effect. We found that in all subjects, dACC – right hippocampal/amygdala connectivity was positively correlated with the orienting effect. This was significant when controlling for mean RT ($p = 0.006$). Post-hoc tests controlling for mean RT revealed that greater connectivity between these areas associated with slower RT in center cue trials $r(51) = 0.42$ $p = 0.002$, but faster RT in valid cue trials, $r(51) = -0.45$, $p = 0.0007$. In summary, cross-network connectivity at rest of the SN at rest was predictive of ANT performance.

In the NTC group alone, three of the above clusters were present (right IFG – right MTG correlated with alerting, right IFG – right insula correlated with validity, and dACC – right IPL

correlated with conflict), but not statistically significant, while the other two were only present contralaterally (right MFG – right SFG correlated with disengagement and dACC – left parahippocampus correlated with orienting). However, several new clusters emerged that were not present in the analysis of all participants (see Table 3.9). First, we found that right IFG – right superior medial frontal gyrus connectivity was also negatively correlated with disengagement scores. Post-hoc tests showed that greater connectivity between these regions was associated with slower RT in invalid cue trials, $r(16) = 0.42$, $p = 0.08$, but was not associated with RT in center cue trials, $p = 0.37$. Second, right IFG – left paracentral lobule connectivity was also negatively correlated with disengagement scores. This was driven by faster RT in invalid cue trials $r(16) = -0.59$, $p = 0.01$, but was not associated with RT in center cue trials, $p = 0.63$. Third, bilateral IFG connectivity was positively correlated with the validity effect. Post-hoc tests correcting for mean RT showed that greater connectivity between these areas was associated with slower RT in invalid cue trials, $r(16) = 0.42$, $p = 0.08$, but was not correlated with RT in valid cue trials. Lastly, MFG- left putamen connectivity was positively correlated with the orienting effect at a whole brain significance level corrected for multiple comparison and positively correlated with the validity effect at a trend level. Post-hoc tests showed that greater connectivity between these areas associated with slower RT in center cue trials $r(16) = 0.68$, $p = 0.002$, but faster RT in valid cue trials, $r(16) = -0.60$, $p = 0.009$ and invalid cue trials, $r(16) = -0.60$, $p = 0.008$. In summary, the NTC group showed the same relationships between rsFC and behavior as were observed in all subjects, as well as several addtional relationships that may have been obscured by the trauma-exposed groups.

2) Resting-state functional connectivity predicts ANT neural activation. Resting-state functional connectivity within ICNs was significantly predictive of task activation across all conditions, however the connectivity of different nodes within the network predicted activations differentially. To examine whether rsFC connectivity within the VAN predicted neural activation associated with the *Alerting contrast*, we examined rsFC regressors using an IFG seed (see Table 3.10, Table 3.11, Figure 3.7). In all participants, we found that greater right IFG – left IFG rsFC predicted greater activity in the *Alerting contrast* activations including the left IFG and left insula, and greater activity in *all target contrast* activations including the dACC and left IPL. Greater right IFG – left MTG rsFC, however, predicted decreased activity in *Alerting contrast* (ACC, left dLPFC, cerebellum, IFG and hippocampus) and *all target contrast* activations (ACC) in the same contrast, as well as decreased activity in task negative areas (PCC and angular gyrus). Right IFG – right MTG connectivity was not a significant predictor of task activity. In the NTC group alone, right IFG – left IFG connectivity did not predict the same activity as was observed in all participants. Instead, greater right IFG – left IFG rsFC predicted greater left angular gyrus activity, an area that was deactivated during the task. Right IFG – left MTG rsFC, however did predict activity in some of the same regions as was observed in all participants, but they were not statistically significant. In summary, rsFC between nodes of the VAN differentially predicted neural activity during *Alerting.*

To examine whether rsFC connectivity within the DAN predicted neural activation associated with the *Orienting contrast*, we examined rsFC regressors within the DAN using an MFG seed (see Table 3.12, Table 3.13, Figure 3.8). In all participants, we found that greater right MFG – right IPL rsFC predicted greater activity in task positive regions including those

involved in responding to targets (mid cingulate, SMA and left precentral gyrus), those involved in visual processing (cuneus, precuenus and superior occipital gyrus) and those involved in cue processing (pons and red nucleus of the midbrain). In the NTC group alone, right IFG – right IPL rsFC remained a robust predictor of activity during orienting for visual processing areas (precuenus) and target processing areas (mid cingulate, dACC and left precentral gryus), with additional peaks emerging in the left insula, putamen and rostral ACC. Activity was not, however, observed in the brainstem. Right IFG – left IFG and left SPL connectivity was not a significant predictor of task activity in all participants or in the NTC group alone. In summary, only rsFC between the right MFG and right IPL was a significant predictor of brain activation during *Orienting.*

To examine whether rsFC connectivity within the VAN and DAN predicted neural activation associated with the *Validity contrast*, we examined rsFC regressors within the VAN and DAN using IFG and MFG seeds, respectively (see Table 3.14, Table 3.15, Figure 3.9). In all participants, we found that greater right IFG – left IFG rsFC predicted decreased activity in *Validity contrast* activations (areas that were more activated for invalid than valid targets: right MFG and IFG) and *Validity contrast* deactivations (areas that were more activated for valid than invalid targets: cerebellum, fusiform, midbrain, and hippocampus. Many of these clusters were present in the NTC group alone, but were not statistically significant, however a new cluster emerged in the left superior temporal gyrus, which was significant at the whole brain level, but not present in the analysis of all participants. Additionally, in all participants, right MFG – right IPL rsFC predicted decreased activity in *Validity contrast* deactivations (areas that were more activated for valid than invalid targets: cerebellum, hippocampus, fusiform, left precentral gyrus

and caudate), but extended into areas not activated by the task (PCC, postcentral gyrus and amygdala). In the NTC group alone, the same clusters were present, but only activity in the caudate remained significant after correction for multiple comparisons. No other contrasts were significant. In summary, rsFC within the VAN and DAN both predicted decreased activity in areas associated with the VAN and DAN during *Validity*.

To examine whether rsFC connectivity within the VAN and DAN predicted neural activation associated with the *Disengagement contrast*, we examined rsFC regressors within the VAN and DAN using IFG and MFG seeds, respectively (see Table 3.16, Table 3.17, Figure 3.10). We found that both greater right IFG – left MTG and right MFG – right IPL rsFC predicted decreased activity in task negative areas including the PCC, mid cingulate gyrus and mPFC, as well as deceased activity in the amygdala, postcentral gyrus and anterior caudate, areas not activated by the task. With the exception of the amygdala, these clusters were present in the analysis of the NTC group alone, with activity in the left postcentral gyrus (extending to the insula and putamen) and mid cingulate gyrus remaining statistically significant after correction for multiple comparisons. On the other hand, greater right IFG – left IFG rsFC predicted greater activity in the postcentral gyrus and surrounding white matter. However, this cluster was not present in the analysis of the NTC group alone. No other contrasts were significant. In summary, rsFC within the VAN and DAN both predicted decreased DMN activity during *Disengagement.*

To examine whether rsFC connectivity within the SN predicted neural activation associated with *Conflict contrast*, we examined rsFC regressors within SN using a dACC seed (see Table 3.17, Table 3.18, Figure 3.11). In all participants, we found that both greater dACC –

right insula and dACC – right amygdala predicted greater activity in *all target contrast* activations including the bilateral cuneus, inferior and superior parietal lobule, SMA, MFG and midbrain. In the NTC group alone, only relationship between dACC – right insula rsFC and task activity remained present. Greater dACC – left insula rsFC, however, predicted decreased activity in visual processing areas including the bilateral cuneus, middle and superior occipital gyri and part of the bilateral precuneus that was more anterior and dorsal to that activated by the task. These clusters were present in the NTC group alone, but were not statistically significant after correction for multiple comparisons. DACC – left amygdala rsFC did not significantly predict task activity. In summary, rsFC between the dACC and bilateral insula was a better predictor of brain activity during *Conflict* than rsFC between the dACC and bilateral amygdala.

3) Resting-state functional connectivity predicts on-task connectivity. Resting-state functional connectivity within ICNs was significantly predictive of on-task functional connectivity across all contrasts, however nodes within the network predicted connectivity differentially (see Table 3.20, Table 3.21). To examine whether rsFC connectivity within the VAN predicted neural connectivity associated with the *Alerting contrast*, we examined the correlation of on-task connectivity using brainstem and right IFG seeds with rsFC using an IFG seed (see Figure 3.7). In all participants, we found that greater right IFG – left IFG rsFC was predictive of greater brainstem – left insula connectivity during *Alerting*, while greater right IFG – left MTG s rsFC was predictive of deceased right IFG – left insula connectivity during *Alerting*. Neither of these relationships were present at all in the analysis of the NTC group only, even at a lower statistical threshold, suggesting that the previous findings were driven by the trauma-exposed groups. In the NTC group, however, right IFG – left IFG was predictive of

greater brainstem connectivity with *Alerting contrast* activated regions including the MFG and inferior parietal sulcus. In all subjects, greater right IFG – left MTG rsFC was also predictive of decreased on-task connectivity between the right IFG and *Alerting contrast* (the SMA, bilateral fusiform, parahippocampus and cerebellum) and *all target contrast* activations (left superior frontal gyrus and left insula). These clusters were present in the NTC group alone, but were not significant after correction for multiple comparisons. Right IFG – right MTG rsFC was not predictive of on-task connectivity during alerting. In summary, rsFC between nodes of the VAN differentially predicted neural connectivity during *Alerting.*

To examine whether rsFC connectivity within the DAN predicted neural connectivity associated with the *Orienting contrast*, we examined the correlation of on-task connectivity using right MFG and inferior parietal seeds with rsFC using a right MFG seed (see Table 3.20, Table 3.21). We found that in both the sample as a whole and the NTC group alone, greater right MFG – right inferior parietal lobule rsFC was predictive of decreased connectivity between the right MFG and several activation peaks for *all cues* (thalamus and pallidum) and *all targets* (precuneus, right supramarginal gyrus and right insula), but did not predict connectivity with peaks activated by the *Orienting contrast* (See Figure 3.8). Additionally, in both the sample as a whole and the NTC group alone, greater right MFG - right inferior parietal rsFC was predictive of decreased connectivity between the right inferior parietal sulcus and the right postcentral gyrus during the task, an area not activated by the *Orienting contrast*. Furthermore, in all participants, greater right MFG – left MFG rsFC was predictive of decreased connectivity between the right inferior parietal lobule and *orienting contrast* activations (MFG, precentral gyrus and SMA), extending into regions not activated during the *orienting contrast* (right IFG

and right insula). These clusters were not present at all in the analysis of the NTC group alone, suggesting the findings may have been driven by the trauma-exposed controls. Lastly, right MFG – left inferior parietal lobule rsFC was not predictive of on-task connectivity during orienting. In summary, rsFC predicted decreased connectivity during the *Orienting contrast* with regions involved and not involved in orienting.

To examine whether rsFC connectivity within the VAN and DAN predicted neural connectivity associated the *Validity contrast*, we examined the correlation of on-task connectivity using right IFG and MFG seeds with rsFC using IFG and MFG seeds (see Table 3.20, Table 3.21). In all participants, resting-state functional connectivity within the VAN and DAN was not predictive of on-task connectivity during *Validity*. In the NTC group alone, however, one relationship at rest emerged as a significant predictor of task connectivity. Specifically, greater right MFG – left IPL rsFC predicted decreased right IFG to left visual processing areas (cuneus and superior occipital gyrus) during the *Validity contrast*. Resting-state connectivity of the VAN, however, was not predictive of task connectivity during validity in the NTC group alone. In sum, rsFC was not predictive of connectivity during *Validity* in all subjects, while rsFC DAN was the only predictor of connectivity in the NTC group.

Discussion

Functional magnetic resonance imaging provides a powerful tool to non-invasively study human brain functioning, making it of interest to those who want to understand brain abnormalities in psychiatric populations. Practically, however, the use of fMRI presents many problems in studying psychiatric populations such as requiring participants to be still for longer periods of time and to have the skills necessary to perform tasks of interest (Rosenberg et al.,

2016). In addition, task-based studies measure changes in small brain activity between conditions but do not reflect baseline levels of activity which could differ in psychiatric populations (Fox & Greicius, 2010). The use of "task-free" or resting-state scans may partially address some of these problems, thus providing a quicker, cheaper and powerful way to understand brain function in psychiatric populations. However, the relationship between connectivity patterns observed at rest and brain function during an active task is largely unknown. Experiment 2 investigated whether patterns of rsFC were predictive of attention task performance, activity and connectivity. If so, this could validate the use of rest as a paradigm to study brain functioning in lieu of task-based studies and could help researchers understand the meaning of aberrant resting-state functional connectivity in psychiatric populations. We had four main findings that are detailed in the paragraphs below. First, we found that the ANT contrasts activated regions of the expected corresponding intrinsic connectivity networks. Second, we found that only certain nodes of rsFC networks were predictive of task-based brain function. Third, we rsFC differentially predicted brain function during cue and target periods. Fourth, surprisingly greater within network connectivity at rest was largely predictive of decreased connectivity during task performance. Finally, we found that SN connectivity was predictive of orienting performance, but rsFC within the specific nodes of the ICNs that we selected, were not predictive of behavioral task performance.

Modified Attention Network Task activates intrinsic connectivity networks

As expected, the modified ANT activated attention regions during the five contrasts we had adopted based on work by Fan et al., (2009). The *Alerting contrast* was associated with activity in the VAN (bilateral inferior parietal lobe, superior temporal gyri, inferior frontal gyri)

and some regions of the DAN and SN (right MFG and ACC). The *Orienting contrast* was associated with activity in the DAN (bilateral superior and inferior parietal lobe, bilateral MFG and superior frontal gyri). The *Validity* and *Disengagement contrasts* were associated with activity in the VAN and DAN, including the right IFG, MFG and TPJ. The *Conflict contrast* was associated with activity in the SMA, which is part of the SN. These findings are consistent with Posner and Petersen's attention model (Petersen & Posner, 2012) and a recent fMRI study which examined a version of the ANT with invalid cues (Xuan et al., 2016). However, brain activation was weaker than expected in the contrasts involving the target processing period. It is possible that because of short duration between the cue and target, we did not fully separate cue and target related activity. We also used a more conservative threshold in our analysis than (Xuan et al., 2016) who implemented a similar version of the ANT to ours (p <0.005 vs. p < 0.01 height threshold). Additionally, our power to detect neural differences was less than that of (Xuan et al., 2016) who had an additional 64 target trials in their version of the ANT. Nevertheless, we still found robust behavioral effects for each ANT component.

Resting-state nodes predict different patterns of task activation.

Our results support our hypothesis that rsFC can predict task activity during a spatial orienting task, however, the connectivity of certain resting-state network nodes were stronger predictors of brain functioning that others (see summary Table 3.22). For rsFC of the VAN, we examined IFG seed connectivity with other nodes of the VAN (left IFG, right and left MTG). Interestingly, connectivity with the right MTG did not predict brain function (activity or connectivity) during any condition that was hypothesized to be involved in the VAN (*Alerting*, *Validity* or *Disengagement*). Instead, only connectivity contralateral was predictive of brain

function. Conversely, for rsFC of the DAN, only right lateralized rsFC was predictive of brain function. Specifically, connectivity of the right MFG with the right IPL was predictive of brain function across all contrasts examined (activity during *Orienting*, *Validity* and *Disengagement* and connectivity during *Orienting* and *Validity*), while connectivity with the left MFG and left SPL was not. In concert, for rsFC of the SN, the strongest predictor of task activity was dACC with right insula connectivity. Specifically, greater rsFC of the dACC with the right insula predicted greater activation of the ACC and bilateral parietal and occipital lobes during *Conflict*, which was statistically significant even in the smaller NTC group alone. Resting-state connectivity of the dACC with the left insula, on the other hand, negatively predicted *Conflict* task activation (superior parietal and mid/sup occipital gyri), but the findings were not significant after correction for multiple comparisons in the smaller NTC group alone. Lastly, SN rsFC connectivity of the dACC to the amygdala was not a strong predictor of task activity. Connectivity with the right amygdala positively predicted *Conflict* task activity in all participants, but these clusters were not present in the analysis of the NTC group alone, possibly hinting that these findings were contributed by aberrant SN rsFC in trauma exposed individuals. Connectivity with the left amygdala did not predict brain function during *Conflict.*

These results support our hypothesis that rsFC can predict task activity and connectivity during a spatial orienting task. This is consistent with prior literature reporting correlations between resting-state and activation during flanker and working memory tasks (Mennes et al., 2010; Zou et al., 2013). Our results are not supporting, however, the notion that these resting state networks, as a whole, participate in their respective attention functions (alerting, orienting,

disengagement and conflict) (Fan & Posner, 2004; Fox, Corbetta, Snyder, Vincent, & Raichle, 2006; Seeley et al., 2007).

There are several reasons why we may have observed relationships only with specific resting-state nodes. Because we simultaneously entered all resting-state connections within a network as regressors into each ANT contrast of interest, one possible explanation is that certain nodes "stole" variance from others. If we had examined connections separately, we may have observed relationships with brain function during the ANT. Because network connections are correlated with one another at rest, however, it made conceptual sense to examine them in one regression. A second explanation for our findings is that resting-state networks contain subnetworks which function differently. Indeed, several reports have described that large scale resting state networks contain subnetworks (Cocchi et al., 2013; Visintin et al., 2015; Yeo et al., 2011). For example, characterizations of the SN (Barrett & Satpute, 2013; Power & Petersen, 2013), have shown that it can be divided into a dorsal subnetwork involved in cognitive control and task set maintenance (Dosenbach et al., 2008), as well as a ventral subnetwork containing the amygdala that is involved in emotional processing, homeostasis and interception (Seeley et al., 2007). Because the ANT is not an affective task, this may explain why we did not observe connectivity with the amygdala. Using a factor analysis, Madhyastha and colleagues (Madhyastha et al., 2015; Madhyastha & Grabowski, 2014), showed that the attention networks can be divided into separate dynamic connections at rest. Consistent with our DAN analysis, they reported that the factor which explained the most variance contained connectivity between the right dorsolateral PFC (dLPFC) and the right IPL, while the factor which explained the least amount of variance contained connectivity between the right dLPFC and the left IPL.

Additionally, visuospatial attention has largely been thought to be lateralized to the right hemisphere (de Schotten et al., 2011). However, right lateralized connectivity within the VAN did not predict brain function during the ANT.

RsFC differentially predicts cue and target processing.

We implemented a modified version of the ANT that allowed us to measure brain functioning during two separate periods of attention processing – the first during the processing of cues (*Alerting* and *Orienting*) and the second during the processing of targets (*Conflict, Validity* and *Disengagement*). Increased activity was observed in all cues and targets relative to baseline in areas consistent with the VAN, DAN, and SN. Decreased activity was observed in all conditions relative to baseline in the PCC and dmPFC, areas consistent with the DMN (Morcom & Fletcher, 2007). Overall, our results support a growing body of literature showing that brain regions can be divided into task positive and task negative groups (Mennes et al., 2010; Uddin, Kelly, Biswal, Castellanos, & Milham, 2009), similar to those observed within ICNs at rest.

We found that rsFC, however, differentially predicted brain function during cue and target periods. Although the VAN is thought to support both alerting and reorienting (Petersen & Posner, 2012; Thiel et al., 2004), connectivity of the right IFG appeared to be play a different role in predicting brain function during cue and target processing. During the *Alerting contrast*, greater right IFG – left IFG connectivity predicted greater task positive activity (dACC, MFG, IFG, inferior parietal lobule and insula) and greater connectivity of areas involved in alerting (brainstem with IFG, MFG, insula, precentral gyrus, cingulate and parietal lobe). During the *Validity contrast*, however, greater connectivity of the right and left IFG predicted decreased

activity in task positive regions (putamen, cerebellum, thalamus, superior temporal gyrus, insula and fusiform). Additionally, greater connectivity of the right IFG with the left MTG predicted less task positive (dLPFC, cerebellum, hippocampus and thalamus) and task negative (PCC) activity during *Alerting* but only less DMN activity during *Disengagement*. Similar to what we observed with the IFG seed, connectivity of the DAN differentially predicted activity during the cue period (*Orienting)* and during target period (*Validity* and *Disengagement*). Greater connectivity of the right MFG with the right IPL during the *Orienting* condition predicted greater brain activation (task positive – cuneus, SMA, pons; task neutral – rACC, postcentral gyrus; task) but also decreased brain activation (task positive – insula, putamen, precentral gyrus, caudate; task neutral – postcentral gyri; task negative – PCC and mPFC) during *Validity* and *Disengagement*.

These results are consistent with the cognitive control model posed by Power and Petersen (Power et al., 2011). These authors describe that during task performance, there are two neural networks that operate on two separate time scales. The first consists of a frontoparietal network, encompassing regions that we have described as the VAN, DAN and FPCN, and the second consists of the dACC and anterior insula in the salience network. They propose that the former operates on a short time scale to respond to initiation cues and moment-to-moment adjustments in task set, whereas the latter is responsible for sustained attention and maintaining the task set throughout the duration of the task. This could explain why VAN and DAN connectivity mostly predicted increased activity during cue periods, but decreased activity during target periods. Supporting this model, we found that only connectivity within the SN predicted increases in activity during target processing. In sum, the ANT is a task which requires the

execution of multiple cognitive operations. Within network connectivity of the VAN and DAN may be important in responding to cues, while within-network connectivity of the SN may be important in responding to targets.

RsFC inversely predicts on-task connectivity.

In contrast with the activation findings, rsFC negatively predicted connectivity during the various contrasts. During *Alerting*, greater connectivity of the right IFG with the left MTG predicted lower on-task connectivity between the right IFG and other task positive regions (MFG, SMA, fusiform, cerebellum, insula and parahippocampus). For *Orienting contrast*, greater right MFG – right IPL rsFC predicted decreased on-task connectivity between the right MFG and multiple task positive areas including the STG, precentral gryus, MFG, thalamus and mid-cingulate cortex and between the right IPL and the right postcentral gyrus (all participants). For the *Validity contrast*, the only predictor of connectivity that emerged was right MFG – left SPL, which negatively predicted connectivity between the right IFG and visual processing areas (cuneus and superior occipital gyrus) in NTC group only.

These findings contrast with what might be expected from the main task effects, in addition to research reporting positive connectivity of attention and sensory motor regions across a variety of attention-related tasks (Duann, Ide, Luo, & Li, 2009; Fan, Hof, Guise, Fossella, & Posner, 2008; Greenberg et al., 2012; Harrison et al., 2005; Pompei, Dima, Rubia, Kumari, & Frangou, 2011; Prado & Weissman, 2011). It is important to note that we are not suggesting these regions were anticorrelated during the task, but that they were *less* correlated than during rest. As this still opposes the results of several papers that have compared resting-state connectivity with task-induced connectivity (Bray, Arnold, Levy, & Iaria, 2015; Elton & Gao,

2015; Rosenberg et al., 2016) our results suggest that the relative degree of connectivity may change during the task, although large scale networks observed at rest remain present during task performance. This may be because flexibility within attention networks is necessary to perform cognitive functions (Bray et al., 2015; Cocchi et al., 2013). Madhyastha and colleagues (2015) proposed that higher connectivity of networks might be a hindrance if the components of the network are responsible for multiple functions, showing that they cannot allocate resources to other areas or that more effort is needed to complete the task. Consistent with this hypothesis, one study (Elton & Gao, 2014) reported decreased coherence of the SN during a selective attention task compared to a state of rest, which was predictive of better behavioral performance. A second study (Tomasi, Wang, Wang, & Volkow, 2014) reported a decrease in the density of functional connectivity during a visual attention task compared to rest. Even increased coupling of the DMN with attention regions has been reported to occur on task compared to rest (Elton & Gao, 2015; Jilka et al., 2014).

Our findings may be specific to the ANT, as some have proposed that ICN relationships are task-dependent (Cocchi et al., 2013). Cole et al. (2013) reported that frontoparietal regions had flexible hubs with changed connectivity with other ICNs across 64 different task states. Similarly, others have reported that on-task connectivity is dependent on the working memory load and complexity of the task (Cocchi et al., 2013; Zou et al., 2013). As the ANT has a relatively low working memory load, this could explain differences between our findings and other studies. However, our on-task connectivity findings should be interpreted with caution as the PPI analysis results without resting-state regressors were weak to begin with. In fact, only

connectivity during the alerting period survived correction for multiple comparisons. Of the two seeds used for this analysis, one – the brainstem - did positively correlate with rsFC.

RsFC between canonical network nodes is not a strong predictor of behavior. Ultimately, we study the brain in order to better understand behavior. However, none of the above findings were predictive of reaction time differences on the ANT. Of the ROIs from our ICN masks, only rsFC of the IFG seed with the right MTG correlated with ANT scores, specifically, larger alerting scores. This was surprising given that connectivity with the right MTG was the only area that did not predict task activation or connectivity. One possible explanation for this finding is that connectivity to the MTG represents attention to auditory stimuli instead of the task at hand. Our MTG cluster overlapped with an area previously found to be involved in auditory, but not visual attention (Braga, Wilson, Sharp, Wise, & Leech, 2013). Since the ANT is a visual task, this could reflect distraction from scanner sounds and slower RT in the absence of cues. Another possibility is that connectivity with this region might be affected in trauma-exposed participants, as it was not found in the analysis of the NTC group alone.

The lack of association of behavior with rsFC in canonical network nodes may seem inconsistent with previous studies that have reported relationships between resting-state ICNs and task performance (Madhyastha et al., 2015; Mennes et al., 2010; Reineberg, Andrews-Hanna, Depue, Friedman, & Banich, 2015; Seeley et al., 2007; Visintin et al., 2015), however, there are several reasons why our findings may differ. First, our seed-based methodology for examining rsFC differed from the ICA and dynamic connectivity approaches used in other studies. It is possible that if we had examined network connectivity within ICNs more broadly, instead of within individual connections with one seed, we may have found different results. For

example, Madhyastha and colleagues (Madhyastha et al., 2015) reported that only connectivity of the left dorsal lateral prefrontal cortex to other nodes was predictive of orienting, something that we did not examine. Another possibility is that modulation of ANT effects is not constrained to individual ICNs. Consistent with this, we found that alerting activated areas of both the DAN and VAN. Madhyastha et al. (2014) reported in an earlier paper that connectivity within the DAN was related to alerting effects, which we did not examine.

Although canonical network nodes did not predict ANT performance, connectivity with other brain areas did appear to modulate ANT effects. Specifically, connectivity with other areas in the networks of interest did predict better performance. Within network connectivity of the DAN was predictive of better orienting and disengagement. In particular, right MFG with left putamen connectivity was associated with faster responses to spatial cues, consistent with literature that has shown putamen to be involved in readiness for motor responses (Kram, Rushwort, Frackowiak, Passingham, & Rushworth, 1998) and spatial attention (de Haan, Morgan, & Rorden, 2008; Xuan et al., 2016). As this finding was only for the NTC group, it suggests possible disruption in trauma-exposed populations groups. Additionally, right IFG – right superior frontal gyrus connectivity predicted faster disengagement from invalidly cued targets, consistent with literature that has implicated the IFG in disengagement (Thiel et al., 2004; Vossel, Thiel, & Fink, 2006) and the superior frontal gyrus in orienting (Boisgueheneuc et al., 2006). Additionally, connectivity of the SN predicted faster conflict resolution, specifically connectivity of the dACC with the right supramarginal gyrus and inferior parietal lobule, consistent with the literature that has found these areas to be involved in task performance and set maintenance (Dosenbach et al., 2008; Power et al., 2011). Finally, dACC connectivity with

the right hippocampus was associated with faster RT to validly cued targets. Although the hippocampus segregates with the DMN at rest, it was activated during orienting in our task and is known to play a role in spatial attention (Chun & Turk-Browne, 2007) and contextual cue learning (Manelis & Reder, 2012).

Connectivity in the VAN, DAN and SN also predicted worse performance. As expected cross-network connectivity of VAN-SN (right IFG with bilateral insula) predicted slower performance in valid cued trials, consistent with the idea that SN may intrude upon networks involved in attention (Block & Liberzon, 2016). As this finding was not present in the analysis of the NTC group alone, it could be specific to trauma-exposed populations or due to a lack of power. Additionally, DAN – DMN (right MFG to bilateral superior medial frontal gyrus) predicted slower RT in center cue trials in all participants, consistent with the hypothesis that DMN suppression is necessary for optimal task performance (Anticevic et al., 2012). Unexpectedly, connectivity of the right IFG with the left IFG (more medial and dorsal than the area in our mask) predicted slower RT in invalidly cued trials. This was surprising because of the VAN's role in reorienting (Thiel et al., 2004; Weissman, Roberts, Visscher, & Woldorff, 2006), but consistent with our other findings that rsFC between these areas predicted decreased task activation and connectivity. It is possible that connectivity with other areas, such as the TPJ or DAN are necessary for successful reorienting and disengagement (Vossel et al., 2012) or that only right lateralized connectivity is involved in reorienting (Kucyi et al., 2012).

Lastly, we partially replicated our findings from Experiment 1, showing that larger orienting effects are associated with greater SN cross-network connectivity. As in Experiment 1, we found that dACC connectivity with the hippocampus was associated with orienting. In

Experiment 1, we interpreted this finding as a reflection of difficulty with disengagement, as it was driven primarily by slowed responses in center cue trials. However, in this study, the correlation with SN connectivity was driven not only by slower responses in center cue trials, but also faster responses in validly cued trials. It is possible that the connectivity with the hippocampus, therefore, is specific to spatial, but not temporal attention. Supporting this idea, we found that the parahippocampus was significantly more active during spatial cues than center cues. We did not replicate our other findings from Experiment 1 regarding cross-network connectivity and orienting performance. Differences in the task design, sample and testing environment could potentially account for these differences.

Limitations.

Several limitations warrant discussion. First, our sample was mostly female and college educated and therefore our findings may not generalize to other populations. Second, our sample included healthy participants as well as those with PTSD. The fact that many of our findings were present in analyses of the entire sample and the non-trauma group alone suggests that they were not driven by trauma exposure. Because this did not apply to all findings, however, replication of our results is necessary with a larger sample of healthy individuals. Third, although the task produced robust behavioral effects, brain activation was weaker than expected in the contrasts involving the target processing period. It is possible that because of short duration between the cue and target, we did not fully separate cue and target related activity or that we did not have a sufficient number of trials to detect activity in the target contrasts. Target related activity was also confounded by the fact that 80% of commission errors occurred on incongruent target trials. However, because overall accuracy on the task was high (over 95%),

we do not believe that the activity observed was solely due to commission errors. Fourth, we were unable to control for eye movements during the task. We did, however, instruct all participants to keep their eyes on the center fixation dot throughout the entire task. Additionally, our DAN findings were not in areas that have been implicated in visual saccades (Braga et al., 2013). Finally, as we employed a seed-based approach to examine rsFC, we only examined the connectivity within *a priori* chosen nodes of each ICN. While we did find significant relationships between rest and task with this approach, it is possible that additional relationships could be elucidated by using a data-driven approach that does not make *a priori* assumptions. Future studies could employ connectomics to examine the relationship of entire ICNs at rest with brain function during task.

Conclusion

In this study, we found that large scale intrinsic connectivity networks present at rest are predictive to the degree of attention task neural activation, connectivity and behavioral performance. However, the relationships we found were very different depending on the task condition, network node and task measure (i.e. activation vs connectivity). This suggests that resting-state might or might not serve as an alternative to active tasks to study brain function, however to do so, much has to be learned regarding the specific ways that resting-state is related to active tasks first.

Chapter III Tables

Table 3.1.
Demographic and clinical characteristics of participants

Characteristic	PTSD (N=24)	TEC (N=19)	NTC (N=20)	$F/t/\chi^2$	*p*
Age, M (SD)	29.83 (10.36)	29.37 (10.89)	29.85 (9.50)	0.403	0.53
Years of education, M (SD)	15.29 (1.99)	15.42 (2.39)	15.93 (2.18)	0.910	0.34
Gender	22 F, 1 M, 1 Other	18 F, 1 M	20 F	2.676	0.61
mTBI, N (%)	6 (25)	5 (26)	2 (10)	2.035	0.36
Race, N (%)				5.765	0.45
White (Non-Hispanic)	16 (67)	14 (74)	15 (75)		
White (Hispanic)	1 (4)	1 (5)	1 (5)		
Black (Non-Hispanic)	4 (27)	2 (11)	3 (15)		
Black (Hispanic)	0	0	1 (5)		
Asian American	0	1 (5)	0		
Mixed Race	3 (13)	1 (5)	0		
CAPS, M (SD)	37.63 (9.87)	1.74 (2.79)	N/A	15.335	<0.001
Trauma type N (%)					
Interpersonal	19 (79)	6 (32)	N/A	8.009	0.005
Physical assault	5	3			
Sexual assault	12	1			
Captivity	1	1			
Homicide	1	1			
Non-interpersonal	5 (21)	11 (68)			
Car accident	2	1			
Life-threatening illness or injury	2	1			
Sudden death	1	2			
Serious accident	0	2			
Suicide	0	5			
Comorbidities, N (%)					
Current depression	14 (58)	0	0		
Past depression	17 (71)	0	1 (5)		
Past hypomania	1 (4)	1 (5)	0		
OCD	3 (13)	0	0		
Panic disorder	4 (17)	0	0		
Agoraphobia	3 (13)	0	0		
Generalized anxiety	8 (33)	0	0		
Social phobia	5 (21)	0	0		
ADHD	2 (8)	0	0		
Learning disability	2 (8)	0	0		

Medical conditions N (%)	9 (38)	4 (20)	3 (16)	3.186	0.20
Psychiatric medications N (%)	10 (42)	0	0		
Non-psychiatric mediations N (%)	8 (33)	8 (42)	7 (35)	0.381	0.82

Note. ADHD, attention-deficit-hyperactivity disorder; CAPS, clinical administered PTSD scale; mTBI, mild traumatic brain injury; NTC, non-trauma-exposed control; OCD, obsessive compulsive disorder; PTSD, posttraumatic stress disorder; TEC, trauma-exposed control

Table 3.2.

Neural activation during the ANT in all participants

Contrast	Brain Region	Cluster size	MNI coordinates (x y z)	Analysis (z)	*p* (FWE) whole brain
Alerting	Bilateral occipital lobe, inf mid and sup temp gyrus, bilateral IFG, MFG, precuneus, cuneus, L precentral gyrus, brainstem, thalamus, inf and sup parietal lobe, SMA, dACC, R insula, putamen, parahipp	9173	-42 -73 -2	>8	<0.001
	Corpus callosum, PCC	136	6 -25 24	5.49	0.023
Orienting	Precuneus, bilateral mid/sup occipital gyrus, L SMA, bilateral sup parietal lobe, sup frontal gyrus, parahipp, cuneus, R inf parietal lobe, angular gyrus, L precentral gyrus, L MFG	2898	24 -55 52	6.55	<0.001
	R MFG, precentral gyrus, postcentral gyrus	262	30 -1 49	5.89	<0.001
Conflict	SMA	41	9 14 64	3.82	0.647
Validity	R mid/sup occipital gyrus, R mid/sup temp gyrus	225	15 -88 4	4.00	0.003
	R MFG	73	36 5 43	3.95	0.274
	L MFG/precentral gyrus	63	-45 -4 43	3.81	0.380
	SMA	63	-6 8 52	3.74	0.380
	R IFG	44	33 26 -2	3.22	0.665
Disengage	R IFG	18	36 23 -17	3.68	0.985
	R IFG	23	48 23 -5	3.32	0.952
	R TPJ	6	48 23 -5	3.36	1.00
All Cues	Bilateral MFG, IFG, precuenus, cuneus, sup and inf temp gyrus, mid and sup occipital gyrus, mid cingulate, MFG, SMA, inf and sup parietal lobule, brainstem, thalamus, cerebellum, fusiform, insula, sup frontal gyrus, precuneus, PCC	11664	-42 -73 -2	> 8	< 0.001
	Corpus callosum, PCC	161	6 -25 25	6.28	0.010
All Targets	ACC, SMA, bilateral precentral and postcentral gyrus, insula, putamen, mid and inf occipital gyrus, parahipp, lingual gyrus, inf and sup parietal lobule, MFG, IFG, sup frontal gyrus, thalamus, inf and sup temp gyrus, fusiform, cerebellum, precuneus, hipp, midbrain	23620	24 -49 -23	>8	<0.001

Note. ACC, anterior cingulate cortex; ANT, attention network task; dACC, dorsal anterior cingulate cortex, FWE, family-wise error; hipp, hippocampus; IFG, inferior frontal gyrus; inf, inferior; L, left; MFG, middle frontal gyrus; mid, middle; parahipp, parahippocampus; MNI, Montreal Neurological Institute; PCC, posterior cingulate cortex; R, right; sig, significant, SMA, supplementary motor area; sup, superior; temp; temporal

Table 3.3.

Neural activation during the ANT in NTC group

Contrast	Brain Region	Cluster size	MNI coordinates (x y z)	Analysis (z)	*p* (FWE)
Alerting	R mid/sup temp gyrus, bilateral cuneus and fusiform, L precentral gyrus, bilateral inf/ sup parietal lobe, L postcentral gyrus, R angular gyrus, L IFG, MFG, insula, parahipp	5641	-39 -58 -11	6.30	<0.001
	R IFG, MFG, precentral gyrus, insula, ACC, SMA	1594	48 2 43	5.23	<0.001
	Midbrain, thalamus, caudate, putamen	663	6 -12 4	5.04	<0.001
Orienting	L sup parietal lobule	62	-24 -58 49	4.38	0.242
	R sup parietal lobule	65	24 -58 52	4.00	0.212
	L mid occipital gyrus	72	-30 -76 19	3.78	0.155
	R mid occipital gyrus	82	27 -73 22	4.28	0.099
	R MFG	42	27 -1 49	4.02	0.538
Conflict	No sig clusters				
Validity	R mid/sup occipital	73	27 -73 25	3.67	0.132
	L MFG/precentral gyrus	31	-39 -4 40	3.47	0.781
	R MFG	42	27 -4 46	3.26	0.533
Disengage	R TPJ	43	45 -37 4	3.39	0.608
	R IFG	18	54 32 1	3.21	0.985
All Cues	Bilateral mid occipital gyrus, mid and sup temp gyrus, inf and sup parietal lobule, fusiform, precentral and postcentral gyrus, MFG, PCC, IFG, cerebellum, angular gyrus, parahipp	8661	-36 -58 -11	6.63	<0.001
	Thalamus, midbrain, caudate	877	6 -13 4	5.47	<0.001
	White matter, corpus callosum, PCC	143	6 -40 16	4.83	0.01
	L insula, IFG	110	-27 20 4	4.71	0.035
	Mid temp gyrus	65	51 11 -29	3.98	0.232
	Caudate	72	-9 14 1	3.62	0.172
All Targets	ACC, SMA, bilateral precentral and postcentral gyrus, insula, putamen, mid and inf occipital gyrus, parahipp, lingual gyrus, inf and sup parietal lobule, MFG, IFG, sup frontal gyrus, thalamus, inf and sup temp gyrus, fusiform, cerebellum, precuneus, hipp, midbrain	15042	12 -52 -17	6.47	<0.001

Note. ACC, anterior cingulate cortex; ANT, attention network task; dACC, dorsal anterior cingulate cortex, FWE, family-wise error; hipp, hippocampus; IFG, inferior frontal gyrus; inf, inferior; L, left; MFG, middle frontal gyrus; mid, middle; parahipp, parahippocampus; MNI, Montreal Neurological Institute; PCC, posterior cingulate cortex; R, right; sig, significant, SMA, supplementary motor area; sup, superior; temp; temporal

Table 3.4.

On-task connectivity: PPI results of the ANT in all participants

Contrast	Brain Region	Cluster Size	MNI coordinates (x y z)	Analysis (z)	*p* (SVC)
Alerting IFG seed	R IFG, insula	65	36 20 1	4.81	0.209
	Pons, culmen, cerebellum	182	-15 -40 -26	4.76	0.003
	L mid occipital gyrus	298	-27 -82 22	4.37	<0.001
	Midbrain/thalamus	59	15 -16 -2	4.23	0.266
	R mid temp gyrus	46	48 -70 10	3.95	0.443
	R IFG	31	42 8 28	3.77	0.733
	Mid/sup occipital gyrus	97	33 -79 19	3.54	0.059
Alerting Brainstem seed	Brainstem, R insula, R IFG, R precentral gyrus, R putamen, caudate, parahipp	918	6 -22 -5	6.80	<0.001
	L insula, L putamen	44	-18 5 -2	4.78	<0.001
	R inf parietal lobule	128	60 -43 34	4.30	0.019
	Culmen, cerebellum, L fusiform, L parahipp	157	-9 -49 -11	4.11	0.007
Orienting SPL seed	Brainstem, L parahipp	27	-15 -22 -26	3.64	0.841
Orienting MFG seed	Culmen, cerebellum, hippocampus	22	0 –46 -2	3.32	0.891
	Cuneus	10	21 -76 16	3.43	0.996
	R fusiform	12	30 -61 -2	3.33	0.990
	L mid temp gyrus	11	-30 -70 16	3.26	0.993
Conflict SMA seed	No clusters >5 voxels				
Validity IFG seed	Cerebellum	21	-12 -49 -20	3.42	0.924
Validity MFG seed	R hippocampus	37	27 -28 -8	4.37	0.642
	L mid/sup occipital gyrus, L mid temp gyrus	18	-33 -70 25	3.25	0.940
Disengagement IFG and TPJs seed	No clusters >5 voxels				

Note. ACC, anterior cingulate cortex; ANT, attention network task; IFG, inferior frontal gyrus; inf, inferior; L, left; mid, middle; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; parahipp, parahippocampus; R, right; sup, superior; SVC, small volume correction; temp; temporal; TPJ, temporal-parietal junction

Table 3.5.

On-task connectivity: PPI results of the ANT in NTC group

Contrast	Brain Region	Cluster Size	MNI coordinates (x y z)	Analysis (z)	*p* (SVC)
Alerting IFG seed	L putamen	18	-15 5 1	4.44	0.954
	Midbrain, putamen, thalamus	72	9 -19 -2	4.26	0.178
	R IFG, insula	35	30 29 1	4.11	0.674
	ACC	30	15 20 31	3.90	0.674
	Midbrain, putamen, thalamus	55	-9 -19 -2	3.87	0.340
Alerting Brainstem seed	Brainstem, thalamus, caudate	130	-6 -19 -5	4.65	0.009
Orienting SPL seed	No clusters > 5 voxels				
Orienting MFG seed	R caudate, cingulate gyrus	18	21 -1 19	3.94	0.941
Conflict SMA seed	No clusters >5 voxels				
Validity IFG seed	R fusiform	34	39 -55 20	3.68	0.692
Validity MFG seed	R fusiform	20	36 -43 -23	3.31	0.912
Disengagement IFG seed	No clusters >5 voxels				
Disengagement TPJ seed	No clusters >5 voxels				

Note. ACC, anterior cingulate cortex; ANT, attention network task; IFG, inferior frontal gyrus; inf, inferior; L, left; mid, middle; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; parahipp, parahippocampus; R, right; sup, superior; SVC, small volume correction; temp; temporal; TPJ, temporal-parietal junction

Table 3.6.

Resting-state functional connectivity of VAN, DAN, SN and DMN in all participants

Contrast Map and Brain Region	Cluster Size	MNI Coordinates (x y z)	Analysis (z)	*p* (SVC)
VAN – R IFG seed				
L IFG	137	-45 20 -5	6.85	<0.001
R MTG	134	60 -37 -2	5.45	<0.001
L MTG	107	-60 -34 -2	4.66	<0.001
DAN – R MFG seed				
L MFG	130	-45 2 34	5.70	<0.001
R IPL	102	36 -49 49	4.78	<0.001
L SPL	70	-39 -52 55	3.73	0.002
SN – dACC seed				
L insula/operculum	163	-54 -1 1	6.93	<0.001
R insula/operculum	162	54 -1 4	6.10	<0.001
L amygdala	24	-24 -1 -11	5.13	0.047
R amygdala	34	30 -7 -11	4.85	0.023
DMN – PCC seed				
vmPFC	194	-3 53 -11	6.775.66	<0.001
L hippocampus	135	-21 -19 -17	5.94	<0.001
R hippocampus	85	27 -19 -20		0.001

Note. dACC, dorsal anterior cingulate cortex; corr; correlation; FWE, family-wise error; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; hipp, hippocampus; L, left; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; MTG, middle temporal gyrus; Neg, negative; Pos, positive; sig; significant; R, right; STG, superior temporal gyrus; SVC, small volume correction

Table 3.7.
Resting-state functional connectivity of VAN, DAN, SN and DMN in NTC group

Contrast Map and Brain Region	Cluster Size	MNI Coordinates (x y z)	Analysis (z)	*P* (SVC)
VAN – R IFG seed				
L IFG	149	-45 20 -5	>8	<0.001
R MTG	146	60 -37 -2	>8	<0.001
L MTG	140	-57 -40 1	>8	<0.001
DAN – R MFG seed				
L MFG	149	-45 2 34	>8	<0.001
R IPL	146	39 -43 43	>8	<0.001
L SPL	119	-30 -52 46	7.65	<0.001
SN – dACC seed				
L insula/operculum	163	-54 -1 1	>8	<0.001
R insula/operculum	163	48 2 7	>8	<0.001
L amygdala	30	-24 -1 -14	6.97	0.003
R amygdala	36	24 2 -14	6.93	0.002
DMN – PCC seed				
vmPFC	194	-6 53 -8	>8	<0.001
L hippocampus	139	-24 -22 -17	>8	<0.001
R hippocampus	97	27 -16 -20	>8	<0.001

Note. dACC, dorsal anterior cingulate cortex; corr; correlation; FWE, family-wise error; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; hipp, hippocampus; L, left; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; MTG, middle temporal gyrus; Neg, negative; Pos, positive; sig; significant; R, right; STG, superior temporal gyrus; SVC, small volume correction

Table 3.8.

Correlation of resting-state functional connectivity with ANT Performance in all participants

Seed	Contrast Map	Brain Region	Cluster Size	MNI Coordinates (x y z)	Analysis (z)	*p* (SVC)
IFG	Pos corr with Alerting	R mid/inf temp gyrus	123	54 -4 -23	4.63	0.037, whole brain
		R amygdala, hippocampus	21	21 -4 -17	3.09	0.200
	Neg corr with Alerting	No sig clusters				
	Pos corr with Validity	dACC	2	-12 -7 40	2.7	0.392
	Neg corr with Validity	L hippocampus	24	-27 -22 -20	3.20	0.068
		R hippocampus	3	24 -13 -23	2.77	0.354
		R posterior insula, postcentral gyrus, precentral gyrus	128	63 -13 22	3.53	0.031, whole brain
		L insula	34	-33 -13 13	3.58	0.917
	Pos corr with Disengagement	No sig clusters				
	Neg corr with Disengagement	No sign clusters				
MFG	Pos corr with Orienting	R hippocampus	9	15 -16 -11	2.68	0.447
	Neg corr with Orienting	R insula not in SV mask	31 22	42 -37 19 33 -1 13	4.24 4.15	0.954 0.996 whole brain
	Pos corr with Validity	Substantia nigra	102	9 -19 -11	4.02	0.092
	Neg corr with Validity	No sig clusters				
	Pos corr with Disengagement	L insula not in SV mask	38	-30 5 10	4.18	0.867, whole brain
		R insula not in SV mask	74	30 2 -8	3.59	0.276, whole brain
	Neg corr with Disengagement	L SFG, medial frontal gyrus	546	-15 62 40	4.03	<0.001, whole brain
		R STG	11	69 -43 -5	3.11	0.158
		L STG	9	-45 32 -5	2.97	0.186
dACC	Pos corr with Conflict	Lingual gyrus	60	-6 -76 -2	3.74	0.445
	Neg corr with Conflict	R supramarginal gyrus, IPL	271	63 -37 46	5.25	<0.001 whole brain

Pos corr with Orienting	L amygdala	16	-30 -1 -20	3.45	0.097
	R hipp, amygdala, insula	109	30 -13 -20	4.10	0.063 whole brain

Note. ANT, attention network task; dACC, dorsal anterior cingulate cortex; corr; correlation; FWE, family-wise error; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; hipp, hippocampus; L, left; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; MTG, middle temporal gyrus; Neg, negative; Pos, positive; sig; significant; R, right; STG, superior temporal gyrus; SVC, small volume correction

Table 3.9.

Correlation of resting-state functional connectivity with ANT performance in NTC group

Seed	Contrast Map	Brain Region	Cluster Size	MNI Coordinates (x y z)	Analysis (z)	*p* (FWE)
IFG	Pos corr with alerting	R mid/inf temp	37	48 -1 20	3.30	0.821
	Pos corr with Validity	L IFG	111	-45 20 13	4.95	0.034
	Neg corr with validity	R postcentral	3	63 -13 19	3.32	1.00
		R insula, operculum	16	48 -19 22	3.32	1.00
		R operculum	3	45 -4 19	3.36	1.00
	Neg corr with Disengagement	R SPG	626	24 -10 67	4.75	<0.001
		L paracentral lobule	121	-6 -22 82	3.96	0.020
MFG	Pos cor with Orienting	L putamen	108	-18 11 4	4.13	0.031
	Pos corr with Validity	L putamen	77	-15 20 4	3.65	0.139
	Neg corr with Disengagement	R SFG	34	15 71 19	3.93	0.856
dACC	Neg corr with conflict	R supramaringal gyrus, IPL	36	60 -28 46	4.26	0.824
	Pos corr with orienting	L paraphipp	8	-15 5 -38	3.53	1.00

Note. ANT, attention network task; dACC, dorsal anterior cingulate cortex; corr; correlation; FWE, family-wise error; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; hipp, hippocampus; L, left; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; MTG, middle temporal gyrus; Neg, negative; Pos, positive; sig; significant; R, right; STG, superior temporal gyrus; SVC, small volume correction

Table 3.10.

VAN connectivity predictors of neural activation during Alerting in all participants

Resting-state regressor	Brain Region	Cluster size	MNI Coordinates (x y z)	Analysis (z)	*p* (FWE)
R IFG – L IFG Pos	dACC	431	0 35 22	4.95	<0.001
	L IPL	289	-42 –34 25	3.94	0.001
	L MFG, IFG, insula	175	-30 26 13	3.67	0.005
R IFG - L IFG Neg	No sig clusters				
R IFG – R MTG Pos and Neg	No sig clusters				
R IFG – L MTG Pos	No sig clusters				
R IFG – L MTG Neg	ACC, PCC, bilateral angular gyrus, bilateral dLPFC	3039	-27 33 25	5.29	<0.001
	R cerebellum, hipp, thalamus	570	39 -55 -26	4.53	<0.001
	R IFG	90	39 38 -2	4.03	0.102
	R postcentral	105	48-16 22	3.71	0.057

Note. dACC, dorsal anterior cingulate cortex; dLPFC, dorsolateral prefrontal cortex; FWE, family-wise error; hipp, hippocampus; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L, left; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; MTG, middle temporal gyrus; Neg, negative; parahipp, parahippocampus; Pos, positive; PCC, posterior cingulate cortex; R, right; sig, significant; VAN, ventral attention network

Table 3.11.
VAN connectivity predictors of neural activation during Alerting in NTC group

Resting-state regressor	Brain Region	Cluster size	MNI Coordinates (x y z)	Analysis (z)	*p* (FWE)
R IFG - L IFG Pos	L angular gyrus	102	-57 -58 31	3.74	0.033
R IFG – L MTG Neg	PCC	37	3 -46 4	4.19	0.636
	R fusiform, parahipp	89	27 -55 -8	3.76	0.060
	R IFG	28	51 23 -5	3.20	0.840

Note. dACC, dorsal anterior cingulate cortex; dLPFC, dorsolateral prefrontal cortex; FWE, family-wise error; hipp, hippocampus; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L, left; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; MTG, middle temporal gyrus; Neg, negative; parahipp, parahippocampus; Pos, positive; PCC, posterior cingulate cortex; R, right; sig, significant; VAN, ventral attention network

Table 3.12.

DAN connectivity predictors of neural activation during Orienting in all participants

Resting-state regressor	Brain Region	Cluster size	MNI Coordinates (x y z)	Analysis (z)	*p* (FWE)
R MFG – L MFG Pos and neg	No sig clusters				
R MFG – R IPL Pos	Bilateral cuneus, sup occipital gyrus, precuneus	262	18 –88 19	4.12	<0.001
	mid cingulate, SMA, L precentral gyrus	461	-9 -25 46	4.02	<0.001
	Pons, red nucleus, brainstem	125	-12 –16 –5	3.77	0.025
R MFG – R IPL neg	No sig clusters				
R MFG – L SPL pos and neg	No sig clusters				

Note. dACC, dorsal anterior cingulate cortex; DAN, dorsal attention network; FWE, family-wise error; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L, left; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; MTG, middle temporal gyrus; Neg, negative; Pos, positive; R, right; rACC, rostral anterior cingulate cortex; sig, significant; SPL, superior parietal lobule; vmPFC, ventromedial prefrontal cortex

Table 3.13.

DAN connectivity predictors of neural activation during Orienting in NTC group

Resting-state regressor	Brain Region	Cluster size	MNI Coordinates (x y z)	Analysis (z)	*p* (FWE)
R MFG – L MFG Pos and neg	No sig clusters				
R MFG – R IPL Pos	vmPFC, rACC	191	9 41 1	5.56	0.001
	mid-cingulate, precuneus	347	0 -13 40	4.43	<0.001
	L insula, putamen	143	-36 17 16	4.33	0.004
	dACC, medial superior frontal gyrus	181	9 47 31	4.16	0.001
	L pre and postcentral gyri	182	-30 -34 49	3.80	0.001
R MFG – R IPL pos and neg	No sig clusters				
R MFG – L SPL pos and neg	No sig clusters				

Note. dACC, dorsal anterior cingulate cortex; DAN, dorsal attention network; FWE, family-wise error; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L, left; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; MTG, middle temporal gyrus; Neg, negative; Pos, positive; R, right; rACC, rostral anterior cingulate cortex; sig, significant; SPL, superior parietal lobule; vmPFC, ventromedial prefrontal cortex

Table 3.14.

VAN and DAN connectivity predictors of neural activation during Validity in all participants

Resting-state regressor	Brain Region	Cluster size	MNI Coordinates (x y z)	Analysis (z)	*p* (FWE)
R IFG – L IFG Pos	No sig clusters				
R IFG – L IFG neg	L parahipp, cerebellum, fusiform, midbrain	711	-15 -31 -11	4.60	<0.001
	L pre and postcentral gyri	112	-42 -13 37	4.47	0.071
	R MFG, IFG	153	36 14 34	4.05	0.019
	R cerebellum, fusiform, culmen	141	33 -52 -23	3.92	0.028
	R hipp, midbrain	129	15 -25 -8	3.78	0.041
R IFG – R MTG pos and neg	No sig clusters				
R IFG - L MTG pos and neg	No sig clusters				
R MFG – L MFG neg and pos	No sig clusters				
R MFG – R IPL	No sig clusters				
R MFG – R IPL neg	PCC, cerebellum, bilateral hipp, culmen, R fusiform	754	9 -49 10	4.27	<0.001
	R paracentral lobule, L precuneus, R postcentral gyrus	141	6 -31 58	4.06	0.028
	L putamen, parahipp, amygdala, olfactory bulb, caudate	443	-27 -4 -5	4.00	<0.001
L MFG – L SPL pos and neg	No sig clusters				

Note. DAN, dorsal attention network; FWE, family-wise error; hipp, hippocampus; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L, left; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; MTG, middle temporal gyrus; Neg, negative; parahipp, parahippocampus; Pos, positive; R, right; sig, significant; SPL, superior parietal lobule; STG, superior temporal gyrus; VAN, ventral attention network

Table 3.15.

VAN and DAN connectivity predictors of neural activation during Validity in NTC group

Resting-state regressor	Brain Region	Cluster size	MNI Coordinates (x y z)	Analysis (z)	*p* (FWE)
R IFG – L IFG Pos	No sig clusters				
R IFG – L IFG neg	L STG	100	-51 -22 10	4.03	0.018
	R insula	39	24 23 -5	3.39	0.480
	R cerebellum, fusiform	18	24 -52 -14	2.80	0.968
R IFG – R MTG pos and neg	No sig clusters				
R IFG - L MTG pos and neg	No sig clusters				
R MFG – L MFG neg and pos	No sig clusters				
R MFG – R IPL pos	No sig clusters				
R MFG – R IPL neg	Precuneus	13	12 -43 13	3.27	0.996
	R paracentral lobule, L precuneus, R postcentral gyrus	56	6 -31 58	3.98	0.191
	caudate	109	-3 2 1	3.92	0.011
	L insula	10	-42 -10 7	3.45	1.00
R MFG – L SPL pos and neg	No sig clusters				

Note. DAN, dorsal attention network; FWE, family-wise error; hipp, hippocampus; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L, left; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; MTG, middle temporal gyrus; Neg, negative; parahipp, parahippocampus; Pos, positive; R, right; sig, significant; SPL, superior parietal lobule; STG, superior temporal gyrus; VAN, ventral attention network

Table 3.16.
VAN and DAN connectivity predictors of neural activation during Disengagement in all participants

Resting-state regressor	Brain Region	Cluster size	MNI Coordinates (x y z)	Analysis (z)	*p* (FWE)
RIFG – L IFG pos and neg	No sig clusters				
R IFG – R MTG pos	White matter, R postcentral gyrus	111	24 -16 34	3.36	0.049
R IFG – R MTG neg	No sig clusters				
R IFG - L MTG pos	No sig clusters				
R IFG – L MTG neg	R hipp, fusiform	195	39 -34 -11	4.66	0.003
	R dACC, caudate	270	18 -1 25	4.49	<0.001
	Precuneus, PCC, cuneus	446	-9 -61 25	4.48	<0.001
	L caudate, ventricle	156	-15 17 16	4.23	0.01
R MFG – L MFG neg and pos	No sig clusters				
R MFG – R IPL	No sig clusters				
R MFG – R IPL neg	mPFC	248	9 53 -5	4.74	0.001
	Precuneus	625	0 -62 22	4.71	<0.001
	Bilateral postcentral gyri, mid-cingulate,	789	-15 -25 46	4.11	<0.001
	R hipp, parahipp, amygdala, fusiform	110	36 -4 -38	3.83	0.051

Note. dACC, dorsal anterior cingulate cortex; DAN, dorsal attention network; FWE, family-wise error; hipp, hippocampus; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L, left; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; mPFC, medial prefrontal cortex; MTG, middle temporal gyrus; Neg, negative; parahipp, parahippocampus; Pos, positive; R, right; sig; significant; SMA, supplementary motor area; SPL, superior parietal lobule; VAN, ventral attention network

Table 3.17.

VAN and DAN connectivity predictors of neural activation during Disengagement in NTC group

Resting-state regressor	Brain Region	Cluster size	MNI Coordinates (x y z)	Analysis (z)	*p* (FWE)
R IFG – L IFG R IFG – R MTG Pos and neg	No sig clusters				
R IFG - L MTG pos	No sig clusters				
R IFG – L MTG neg	R hipp, fusiform	8	39 -34 -11	2.91	1.000
R MFG – L MFG neg and pos	No sig clusters				
R MFG – R IPL pos	No sig clusters				
R MFG – R IPL neg	mPFC	77	12 47 4	3.65	0.118
	Precuneus, PCC	70	3 -58 25	3.45	0.162
	L insula, postcentral gyrus, putamen, operculum, precentral gyrus	203	-24 -7 13	3.90	0.001
	mid-cingulate, paracentral lobule, SMA	127	15 -7 43	3.63	0.014
R MFG - L SPL pos and neg	No sig clusters				

Note. dACC, dorsal anterior cingulate cortex; DAN, dorsal attention network; FWE, family-wise error; hipp, hippocampus; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L, left; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; mPFC, medial prefrontal cortex; MTG, middle temporal gyrus; Neg, negative; parahipp, parahippocampus; Pos, positive; R, right; sig; significant; SMA, supplementary motor area; SPL, superior parietal lobule; VAN, ventral attention network

Table 3.18.

SN (dACC seed) connectivity predictors of neural activation during Conflict in all participants

Resting-state regressor	Brain Region	Cluster size	MNI Coordinates (x y z)	Analysis (z)	*p* (FWE)
L insula pos	No sig clusters				
L insula neg	Bilateral precuneus, SPL	219	-15 -46 61	4.02	0.002
	bilateral cuneus, mid/sup occipital gyri	188	-9 -88 25	3.92	0.004
R insula pos	Bilateral cuneus, precuneus, IPL, postcentral gyrus, SPL, MFG, precentral gyrus, SMA, L mid occipital, R sup occipital, sup frontal gyri	2895	-30 -4 58	4.84	<0.001
	R supramarginal gyrus, IPL	78	54 -34 31	3.88	0.085
L amy pos and neg	No sig clusters				
R amy neg	No sig clusters				
R amy pos	R angular gyrus, R IPL, R SPL, R mid occipital, R precuneus, R MTG	250	39 -55 34	3.93	0.001
	PCC	123	0 -40 19	3.88	0.034
	L mid/sup occipital, SPL, precuneus	196	-9 -79 46	3.82	0.003
	Midbrain, pons	122	-6 -22 -29	3.74	0.036

Note. ACC, anterior cingulate cortex; amy; amygdala; dACC, dorsal anterior cingulate cortex; FWE, family-wise error; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L, left; MFG, middle frontal gyrus; mid, middle; MNI, Montreal Neurological Institute; MTG, middle temporal gyrus; Neg, negative; PCC, posterior cingulate cortex; Pos, positive; R, right; sig, significant; SMA, supplementary motor area; SPL, superior parietal lobule; sup, superior

Table 3.19.

SN (dACC seed) connectivity predictors of neural activation during Conflict in NTC group

Resting-state regressor	Brain Region	Cluster size	MNI Coordinates (x y z)	Analysis (z)	*p* (FWE)
L insula pos	No sig clusters				
L insula neg	L SPL	5	-18 -43 61	3.11	1.000
	bilateral cuneus	7	-6 -88 19	3.10	1.00
		15	9 -79 19	3.27	0.994
R insula pos	ACC, SMA	110	15 8 34	4.33	0.037
	R MFG	28	30 -1 55	3.20	0.872
	L MFG	30	-27 2 61	2.92	0.872
	R cuneus, bilateral sup/mid occipital gyrus, L SPL	321	-27 -76 40	3.94	<0.001
	R SPL, R sup occipital, precuenus	79	21 -67 37	3.69	0.014
R insula neg	No sig clusters				
L amy pos and neg	No sig clusters				
R amy pos and neg	No sig clusters				

Note. ACC, anterior cingulate cortex; amy; amygdala; dACC, dorsal anterior cingulate cortex; FWE, family-wise error; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L, left; MFG, middle frontal gyrus; mid, middle; MNI, Montreal Neurological Institute; MTG, middle temporal gyrus; Neg, negative; PCC, posterior cingulate cortex; Pos, positive; R, right; sig, significant; SMA, supplementary motor area; SPL, superior parietal lobule; sup, superior

Table 3.20.

Resting-state connectivity predictors of functional connectivity during the ANT in all participants

PPI contrast and seed	Resting-state regressor	Brain Region	Cluster size	MNI Coordinates (x y z)	Analysis (z)	*p* (FWE)
Alerting Brainstem	R IFG - L IFG pos	L insula	184	-36 -16 10	4.03	0.004
	R IFG - L IFG neg	No sig clusters				
	R IFG – R and L MTG pos and neg	No sig clusters				
Alerting IFG	R IFG – L IFG R IFG - R MTG pos and neg	No sig clusters				
	R IFG – L MTG pos	No sig clusters				
	R IFG – L MTG neg	L MFG, SFG	200	-33 47 19	4.76	0.002
		SMA	266	12 14 55	4.70	<0.001
		L fusiform, cerebellum, parahipp, mid occ gyrus	471	-39 -40 -20	4.22	<0.001
		L insula	287	-39 11 -5	4.21	<0.001
		R fusiform, parahipp	126	39 -28 -17	5.07	0.029
Orienting MFG	R MFG - L MFG R MFG - L SPL pos and neg	No sig clusters				
	R MFG – R IPL pos	No sig clusters				
	R MFG - R IPL neg	Precuneus	104	9 -49 55	4.47	0.049
		L thalamus, pallidum, midbrain	366	-9 -22 4	4.27	<0.001
		R insula, STG	251	45 -7 -2	4.22	<0.001
		R supramarginal gyrus	94	63 -25 28	3.84	0.073
Orienting SPL	R MFG – L MFG pos	No sig clusters				
	R MFG - L MFG neg	L pre and post central gyri	146	-48 -13 49	4.08	0.019
		SMA	133	0 14 58	3.70	0.029
		L insula, IFG, MFG	232	-45 11 31	3.53	0.001

	R MFG - R IPL pos	No sig clusters				
	R MFG – R IPL neg	R post central gyrus	263	54 -19 40	4.40	0.001
		L post central gyrus	109	-27 -40 58	3.84	0.065
	R MFG – L SPL pos and neg	No sig clusters				
Validity IFG MFG	All resting-state regressors	No sig clusters				

Note. FWE, family-wise error; hipp, hippocampus; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L, left; MFG, middle frontal gyrus; mid, middle; MNI, Montreal Neurological Institute; MTG, middle temporal gyrus; Neg, negative; parahipp, parahippocampus; Pos, positive; R, right; sig, significant; SMA, supplementary motor area; SPL, superior parietal lobule; sup, superior

Table 3.21.

Resting-state connectivity predictors of functional connectivity during the ANT in NTC group

PPI contrast and seed	Resting-state regressor	Brain Region	Cluster size	MNI Coordinates (x y z)	Analysis (z)	*p* (FWE)
Alerting Brainstem	R IFG – L IFG pos	R insula, IFG, MFG, precentral gyrus	269	45 38 10	3.95	<0.001
		L parietal lobe, cingulate, supramarginal gyrus	98	-18 -37 37	3.91	0.034
	RIFG – R and L MTG, pos and neg	No sig clusters				
Alerting IFG	R IFG – L IFG IFG – R MTG pos and neg	No sig clusters				
	R IFG - L MTG pos	No sig clusters				
	R IFG - L MTG neg	MFG, SFG	61	-30 35 22 24 44 19	3.53 3.78	0.320 0.225
		SMA	39	-18 8 67	3.52	0.689
		L sup occipital gyrus	7	-24 -76 31	3.01	1.00
		L STG, insula	20	-48 -10 -8	3.24	0.975
		R hipp	9	30 -25 -8	3.17	1.00
Orienting MFG	R IFG - L MFG R IFG – L SPL Pos and neg	No sig clusters				
	R MFG – R IPL pos	No sig clusters				
	R MFG – R IPL neg	R sup/mid temp gyrus, insula, precentral gyrus, postcentral gyrus	257	45 -7 -14	4.49	<0.001
		Bilateral parahipp, hipp, cerebellum, thalamus, midbrain, fusiform, precuenus	421	-24 -49 -11	3.76	<0.001
		L pallidum, thalamus, midbrain, putamen	92	-12 11 -8	3.73	0.051
		mid-cingulate	18	0 -28 49	3.26	0.979

		R MFG, precentral gyrus, postcentral gyrus, IFG, SFG	149	54 -13 43	3.57	0.004
Orienting SPL	R MFG – L MFG pos and neg	No sig clusters				
	R MFG – R IPL pos	No sig clusters				
	R MFG – R IPL neg	R postcentral gyrus	11	57 -13 46	2.86	0.999
	R MFG - L SPL pos and neg	No sig clusters				
Validity IFG	R MFG – L SPL neg	L cuneus, sup occipital gyrus	158	-24 -73 13	4.32	0.001
Validity MFG	All resting-state regressors	No sig clusters				

Note. FWE, family-wise error; hipp, hippocampus; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L, left; MFG, middle frontal gyrus; mid, middle; MNI, Montreal Neurological Institute; MTG, middle temporal gyrus; Neg, negative; parahipp, parahippocampus; Pos, positive; R, right; sig, significant; SMA, supplementary motor area; SPL, superior parietal lobule; sup, superior

Table 3.22.

Results summary of resting-state functional connectivity predicting task positive, neutral and negative activity and connectivity on the ANT

Resting-state regressor	Activation						PPI			
VAN	Alerting		Validity		Disengage		Alerting Brainstem seed		Alerting IFG seed	
	All subjects	NTC	All subjects	NTC	All subjects	NTC	All subjects	NTC	All subjects	NTC
	+ TP, + TN	+ TN	- TP	-TP			+ TP	+TP		
R IFG – LIFG										
R IFG – R MTG										
R IFG – L MTG	-TP, - TN	-TP, - TN			-TN, - N				-TP	-TN
DAN	Orienting		Validity		Disengage		Orienting MFG and SPL seeds		Validity IFG seed	
	All subjects	NTC	All subjects	NTC	All subjects	NTC	All subjects	NTC	All subjects	NTC
R MFG-L MFG										
R MFG – R IPL	+TP	+TP, +TN	-TP, - N	-TP	-TN, -N	-TP, - TN, -N	-TP, -N	-TP, -N		
R MFG – L SPL										-TP
SN	Conflict									
	All subjects	NTC								
dACC- R insula	+ TP	+TP								
dACC – L insula	-TP, -N	-TP, -N								
dACC – R amy	+TP									
dACC – L amy										

Note. "-" denotes decreased activation/connectivity; "+" denotes increased activation/connectivity. Task positive, negative and neutral are defined as regions activated by the task, deactivated by the task and neither activated nor deactivated by the task. Amy, amygdala; ANT, attention network task; dACC, dorsal anterior cingulate cortex; DAN, dorsal attention network; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L, left; MFG, middle frontal gyrus; N, task neutral; PPI, psychophysiological interaction; R, right; SN, salience network; SPL, superior parietal lobule; TN, task-negative; TP, task-positive, VAN, ventral attention network.

Chapter III Figures

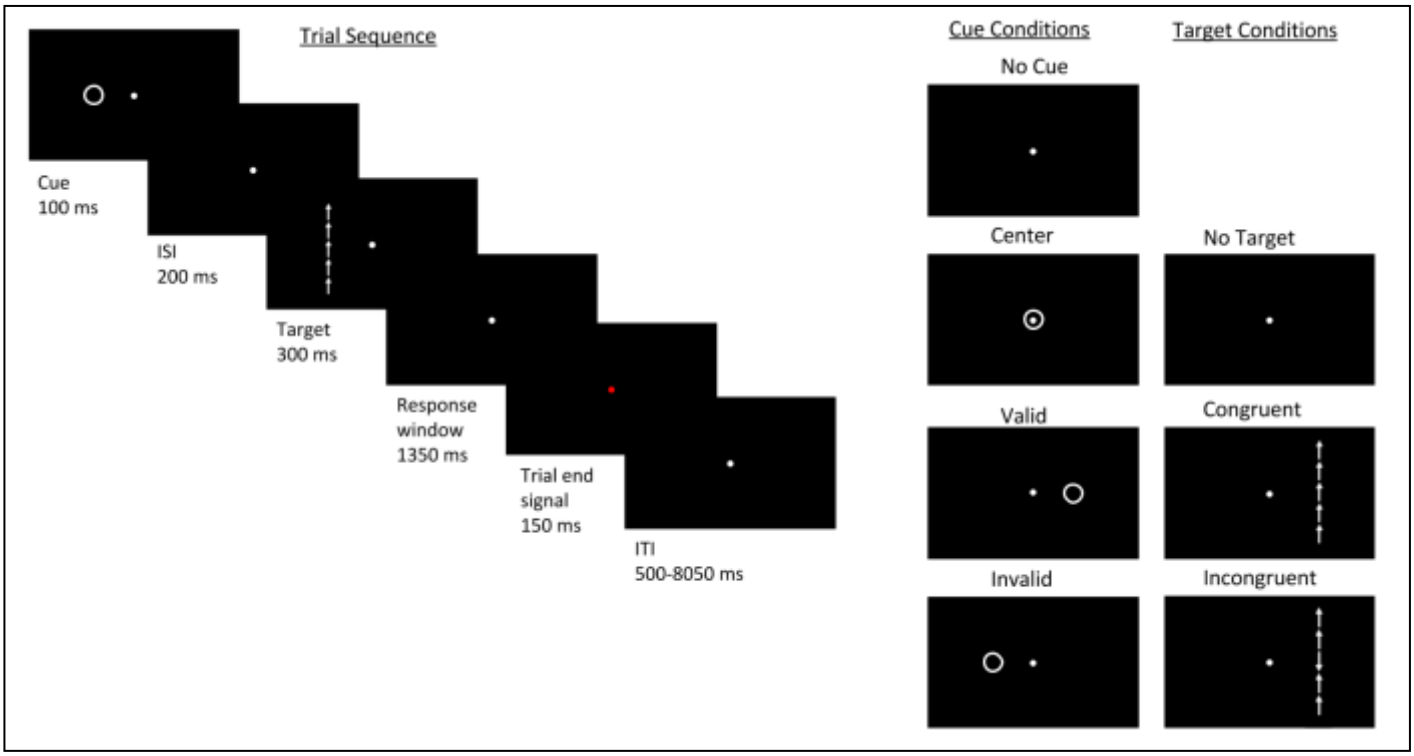


Figure 3.1. Schematic of the Modified Attention Network Task.
ITI, intertrial interval; ms, milliseconds.
To better isolate the processes of disengagement, we modified the original version of the ANT to include both valid and invalid spatial cue trials. 80% of the targets that are preceded by spatial cues were invalid, occurring in the opposite location as the target (Fan et al., 2009). Additionally, there are 36 cue only trials without targets to better isolate cue and target related activity (Ollinger, Shulman, & Corbetta, 2001; Weissman, Warner, & Woldorff, 2004).

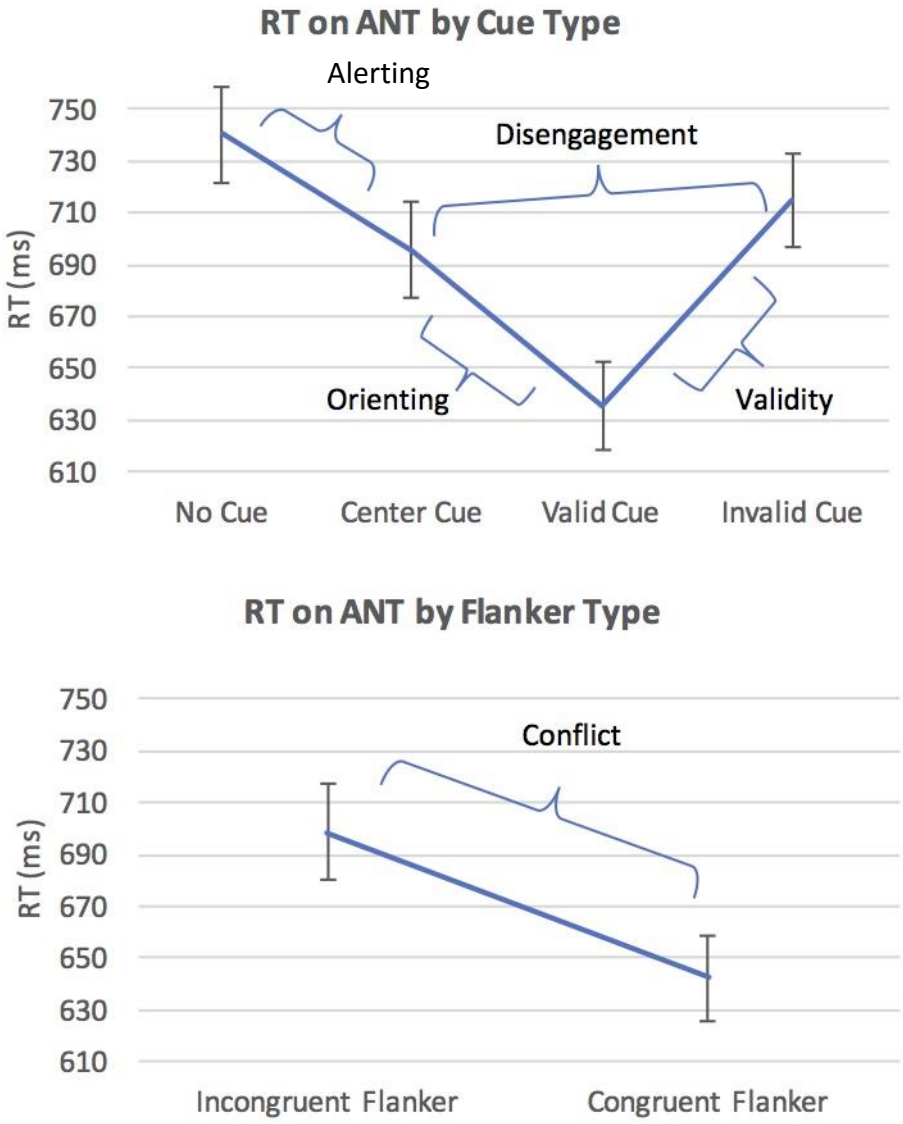


Figure 3.2. ANT effects in all participants.
ANT, attention network task; ms, milliseconds; RT, reaction time.
Within participants t-test revealed significant effects for each of the five ANT components.
Top panel: Alerting (no cue – center cue), $p < 2.2e\text{-}16$; Orienting (valid cue – center cue), $p = 5.4e\text{-}15$; Validity (invalid cue – valid cue), $p < 2.2e\text{-}16$; and disengagement (invalid cue – center cue), $p = 0.0002$.
Bottom panel: Conflict (incongruent flanker – congruent flanker), $p = 6.26e\text{-}16$.

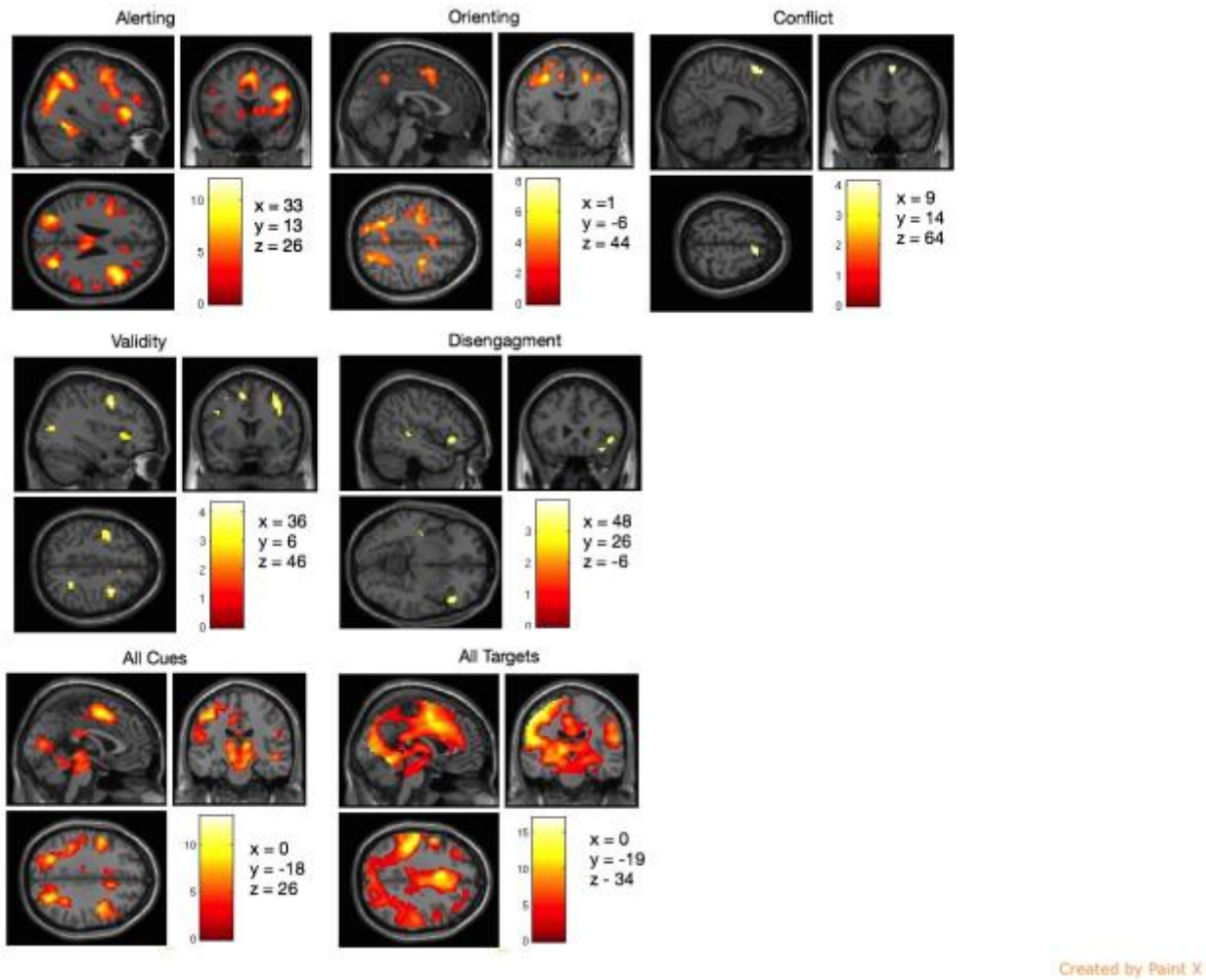


Figure 3.3. Positive brain activation during the Attention Network Task in all participants.
$p < 0.005$ uncorrected
Top row: The *Alerting contrast* (center cue – baseline) was associated with activity in bilateral frontoparietal and occipital regions, as well as the brainstem and anterior cingulate cortex, areas consistent with the ventral attention network. The *Orienting contrast* (spatial cue – center cue) was associated with activity in more dorsal frontoparietal regions, consistent with the dorsal attention network. The *Conflict contrast* (incongruent – congruent flanker) was associated with activity in the supplementary motor area, consistent with the salience network.
Middle row: The *Validity* and *Disengagement contrasts* were associated with activity in the areas consistent with the ventral and dorsal attention networks, including the right inferior frontal gyrus, middle frontal gyrus and temporoparietal junction.
Bottom row: Activations in the contrasts of all cues – baseline and all targets – baseline.

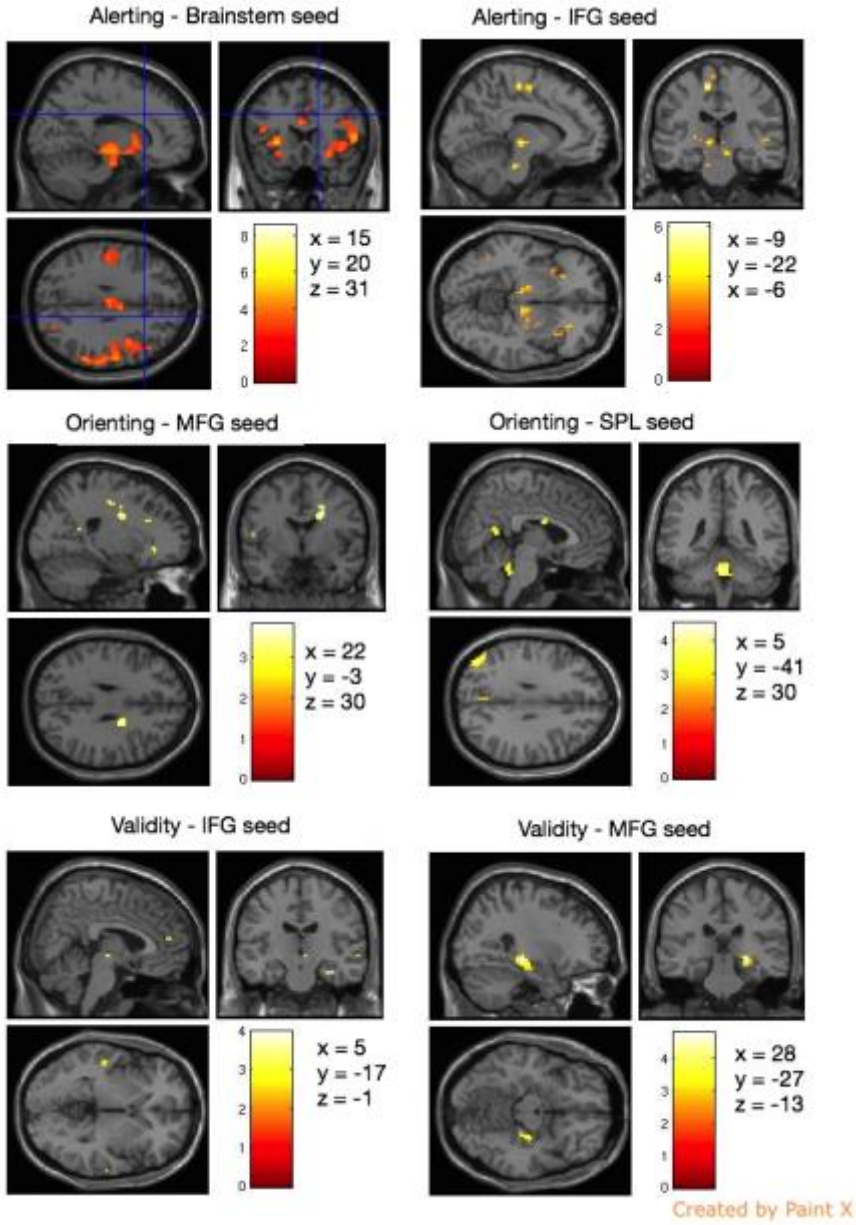


Figure 3.4. Positive connectivity during the Attention Network Task in all participants.
$p < 0.005$ uncorrected. IFG, inferior frontal gyrus; MFG, middle frontal gyrus; SPL, superior parietal lobule.
Top row: Connectivity of the right IFG and brainstem seeds in the *Alerting contrast.* Connectivity was observed between the IFG seed and a) the pons extending to the cerebellum and culmen and b) the bilateral middle occipital gyrus. Connectivity was observed between the brainstem seed and the insula, putamen, cerebellum, inferior parietal lobule, parahippocampus, brainstem and occipital lobe.
Middle row: Connectivity of the right MFG and right SPL seeds in the *Orienting contrast.* Connectivity was observed between the MFG seed and the hippocampus, cerebellum, cuneus, and middle temporal gyrus. Connectivity was observed between the SPL seed and a) the brainstem and b) the parahippocampus.
Bottom row: the right IFG and right MFG seeds for the *Validity contrasts.* Connectivity was observed between the IFG seed and the cerebellum, and between the MFG seed and the hippocampus, occipital lobe and middle temporal gyrus.

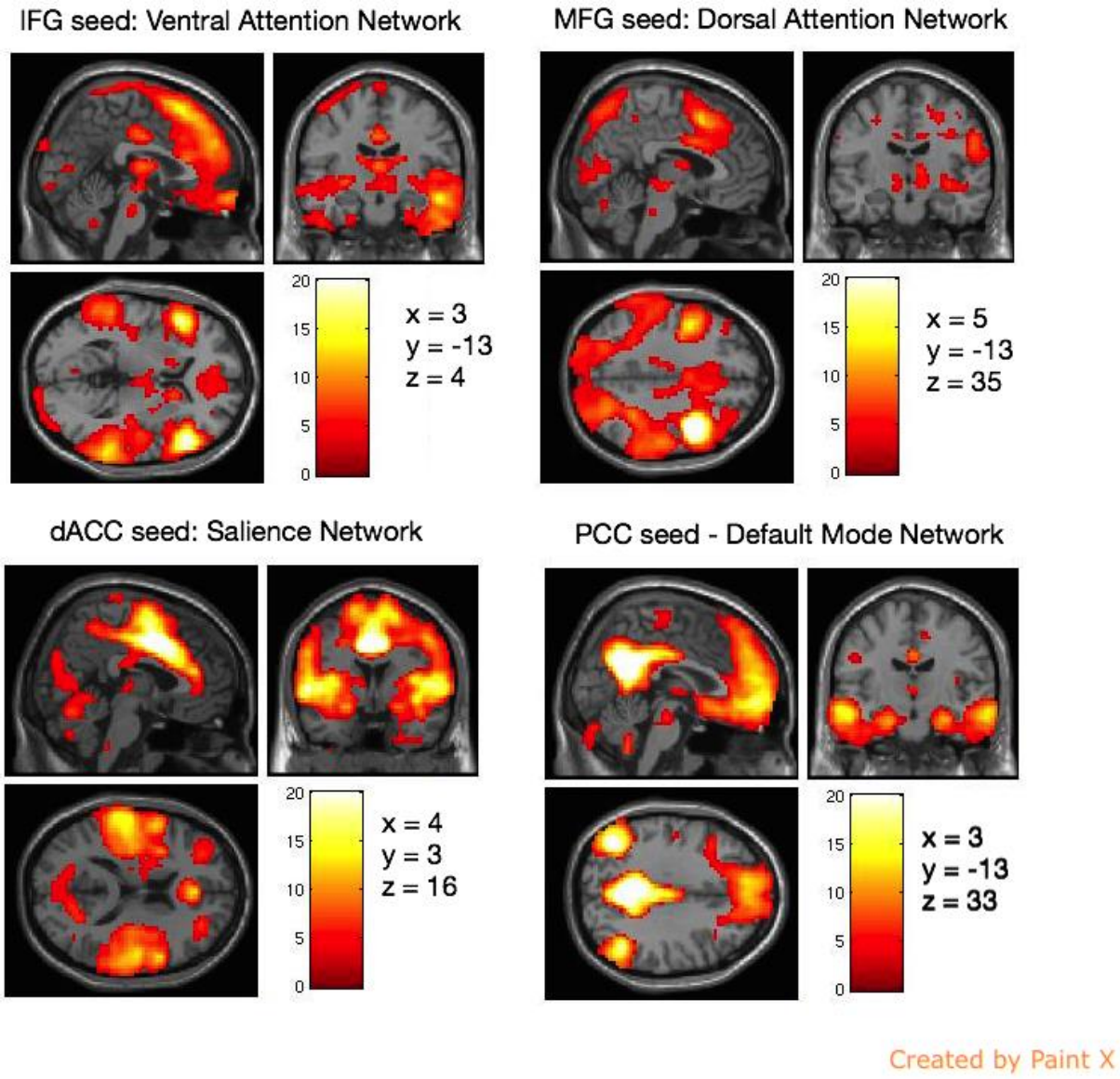


Figure 3.5. Resting-state functional connectivity of intrinsic connectivity networks in all participants. $p < 0.001$ uncorrected. IFG, inferior frontal gyrus; MFG, middle frontal gyrus; dACC, dorsal anterior cingulate cortex; PCC, posterior cingulate cortex. 10-mm-spheres were created around each coordinate based on (De Luca et al., 2006) and positive functional connectivity with each sphere was examined.

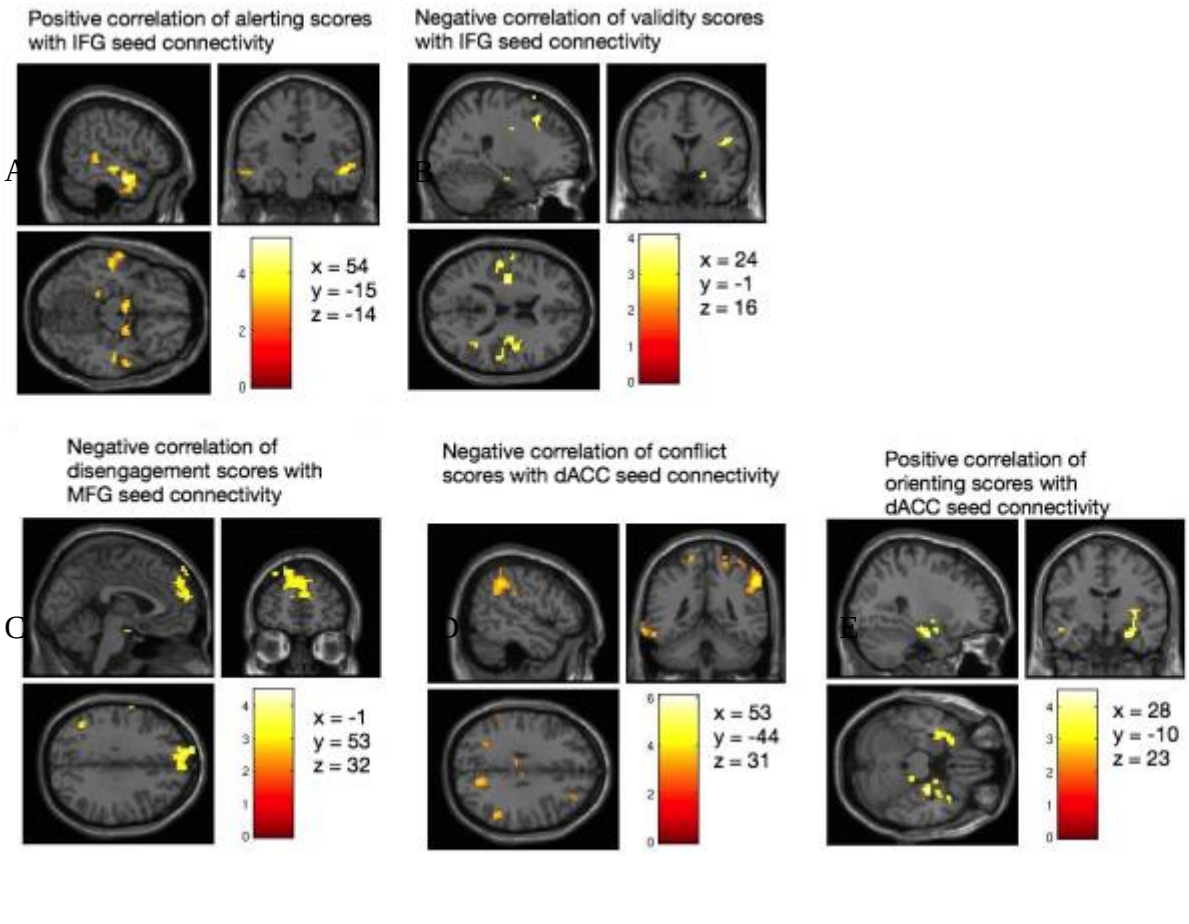


Figure 3.6. Resting-state functional connectivity predictors of behavioral ANT effects (RT differences) in all participants.

$p < 0.005$ uncorrected. IFG, inferior frontal gyrus; MFG, middle frontal gyrus; dACC, dorsal anterior cingulate cortex. A) Right IFG- right middle/inferior temporal gyrus connectivity was positively correlated with alerting scores, driven slower RT in no cue trials, and faster RT in center cue trials. B) right IFG – right insula connectivity was negatively correlated with validity scores, driven by slower RT in valid cue trials and faster RT in invalid cue trials. C) Right MFG- right superior medial frontal gyrus connectivity negatively correlated with disengagement, driven by slower RT in center cue trials. D) dACC - right IPL and supramarginal gyrus connectivity was negatively correlated with conflict scores, driven by faster RT in both incongruent and congruent trials. E) dACC – right hippocampal/amygdala connectivity was positively correlated with the orienting effect, driven by slower RT in center cue trials, but faster RT in valid cue trials.

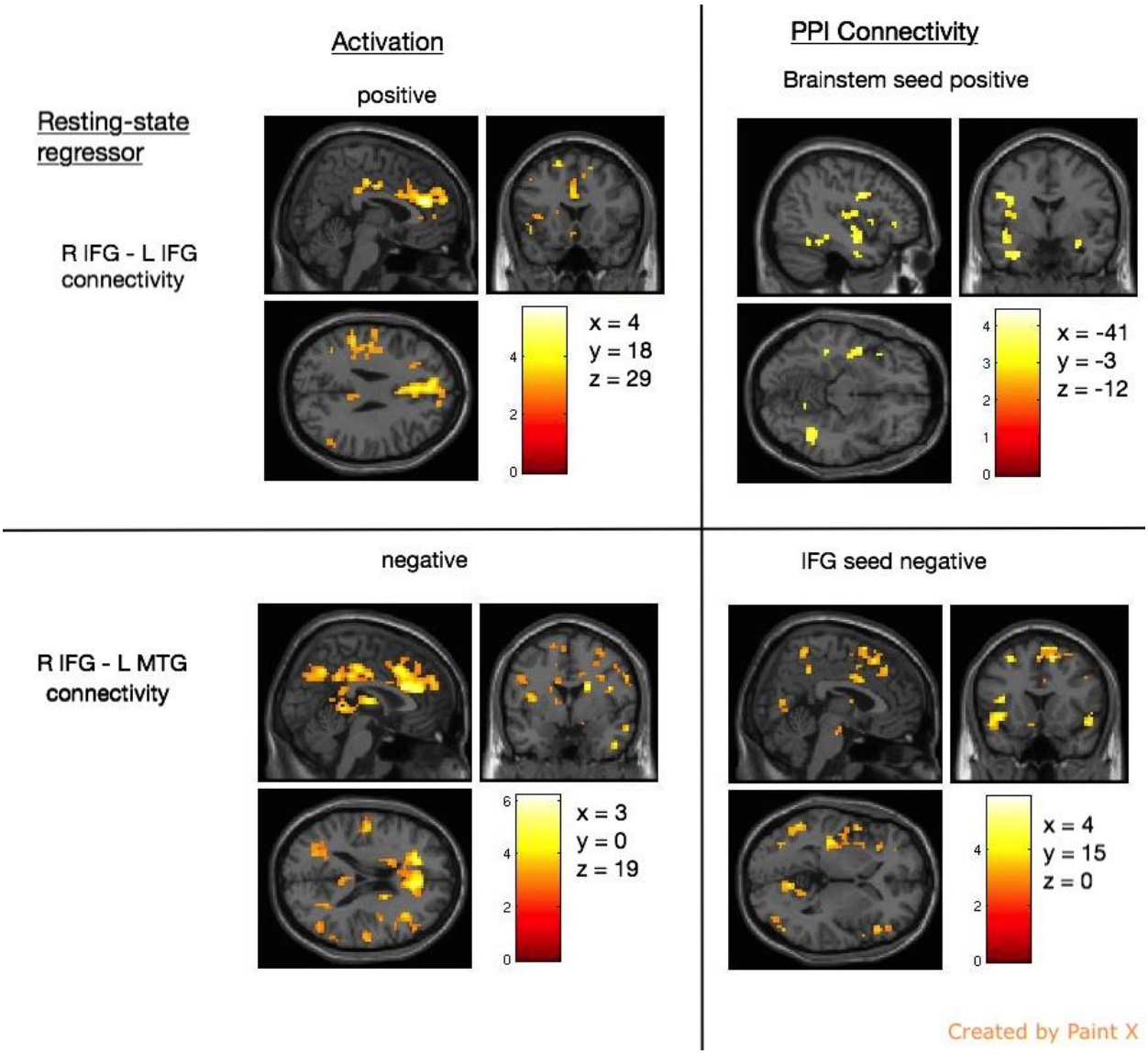


Figure 3.7. Resting-state functional connectivity predictors of brain activity and connectivity during *Alerting* in all participants.

$p < 0.005$ uncorrected. IFG, inferior frontal gyrus; MTG, middle temporal gyrus; R, right; L, left.

Left column: Greater right IFG – left IFG rsFC predicted greater activity the left IFG, left insula, dACC and left IPL. Greater right IFG – left MTG rsFC, however, predicted decreased activity in the ACC, left dLPFC, cerebellum, IFG, hippocampus, PCC and angular gyrus.

Right column: Greater right IFG – left IFG rsFC was predictive of greater brainstem – left insula connectivity during *Alerting*, while greater right IFG – left MTG s rsFC was predictive of deceased right IFG – left insula connectivity during *Alerting*.

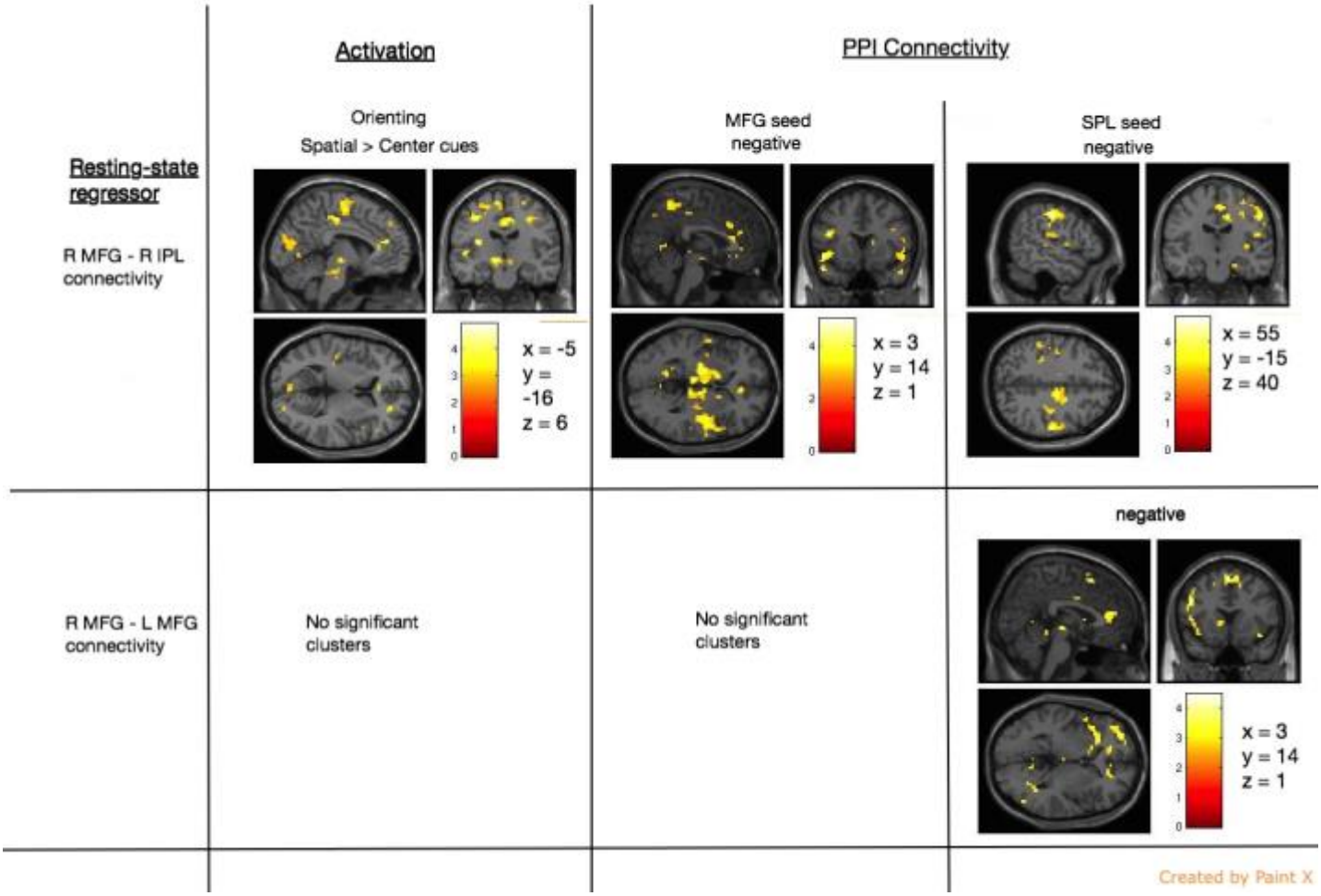


Figure 3.8. Resting-state functional connectivity predictors of brain activity and connectivity during *Orienting* in all participants.

$p < 0.005$ uncorrected. *Note.* IPL, inferior parietal lobule; MFG, middle frontal gyrus; R, right; L, left; SPL, superior parietal lobule; rsFC, resting-state functional connectivity.

Left column: Greater right MFG – right IPL rsFC predicted greater activity in targets processing areas (mid cingulate, SMA and left precentral gyrus), visual areas (cuneus, precuenus and superior occipital gyrus) and cue processing areas (pons and red nucleus of the midbrain) during *Orienting.*

Middle column: Greater right MFG – right IPL rsFC was predictive of decreased connectivity between the right MFG and the thalamus, pallidum, precuneus, right supramarginal gyrus and right insula during *Orienting.*

Right column: Greater right MFG - right IPL rsFC was predictive of decreased connectivity between the right inferior parietal sulcus and the right postcentral gyrus during *Orienting*. Greater right MFG – left MFG rsFC was predictive of decreased connectivity between the right IPL and the MFG, precentral gyrus, SMA, right IFG and right insula during *Orienting*.

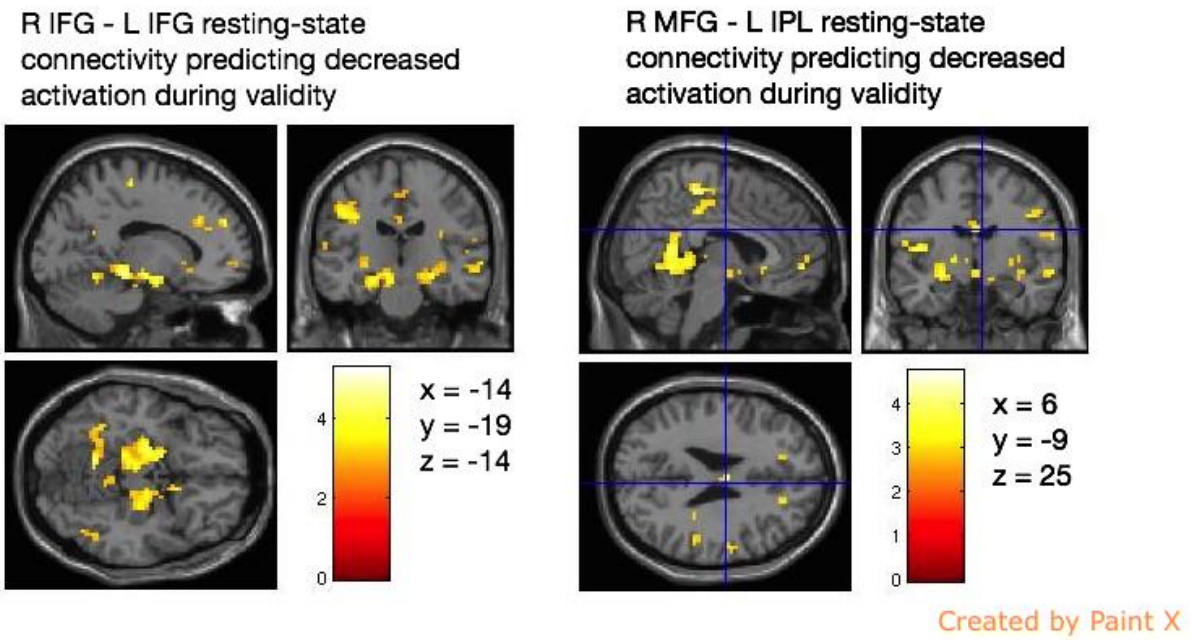


Figure 3.9. Resting-state functional connectivity predictors of brain activity during *Validity* in all participants.

$p < 0.005$ uncorrected. IFG, inferior frontal gyrus; IPL, inferior parietal lobule; MFG, middle frontal gyrus; R, right; L, left; rsFC, resting-state functional connectivity.

Left: greater VAN (right IFG – left IFG) rsFC predicted decreased activity the right MFG, IFG, cerebellum, fusiform, midbrain, and hippocampus in the *Validity* contrast.

Right: greater DAN (right MFG – right IPL) rsFC predicted decreased activity in the cerebellum, hippocampus, fusiform, left precentral gyrus, caudate, PCC, postcentral gyrus and amygdala in the *Validity* contrast.

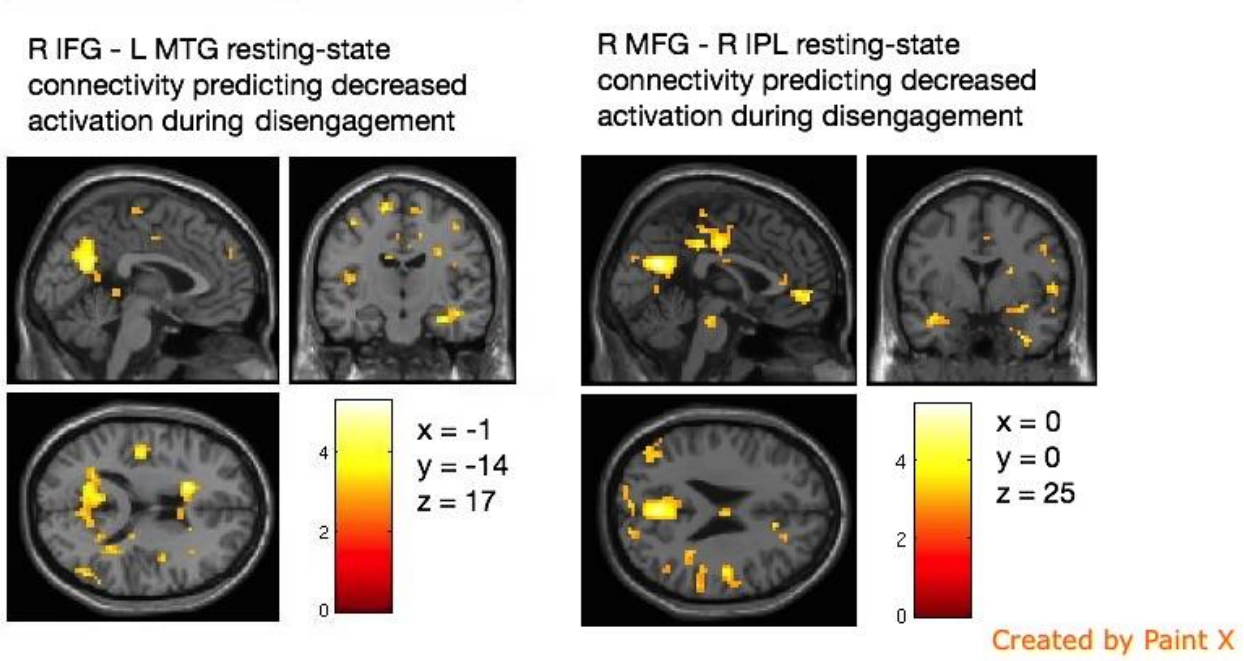


Figure 3.10. Resting-state functional connectivity predictors of brain activity during *Disengagement* in all participants.

$p < 0.005$ uncorrected. IFG, inferior frontal gyrus; IPL, inferior parietal lobule; MFG, middle frontal gyrus; MTG, middle temporal gyrus; R, right; L, left; rsFC, resting-state functional connectivity.

Greater VAN (right IFG – left MTG, left panel) and DAN (right MFG – right IPL, right panel) rsFC predicted decreased activity in task negative areas including the PCC, mid cingulate gyrus and mPFC, as well as deceased activity in the amygdala, postcentral gyrus and anterior caudate, areas not activated by the task in the *Disengagement* contrast.

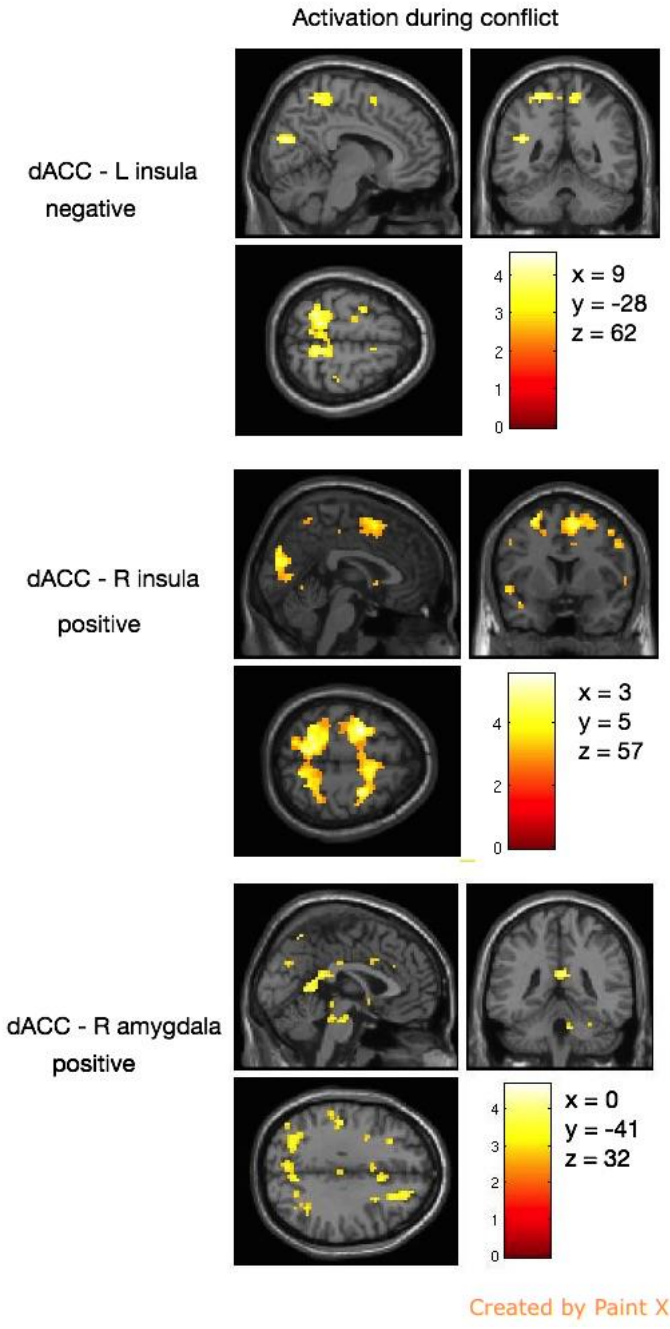


Figure 3.11. Resting-state functional connectivity predictors of brain activity during conflict in all participants.

$p < 0.005$ uncorrected. dACC, dorsal anterior cingulate cortex; R, right; L, left; rsFC, resting-state functional connectivity. Top: Greater dACC – left insula rsFC predicted decreased activity in the bilateral cuneus, middle and superior occipital gyri, and the bilateral precuneus. Middle and bottom: greater dACC – right insula and dACC – right amygdala predicted greater activity in the bilateral cuneus, inferior and superior parietal lobule, SMA, MFG and midbrain.

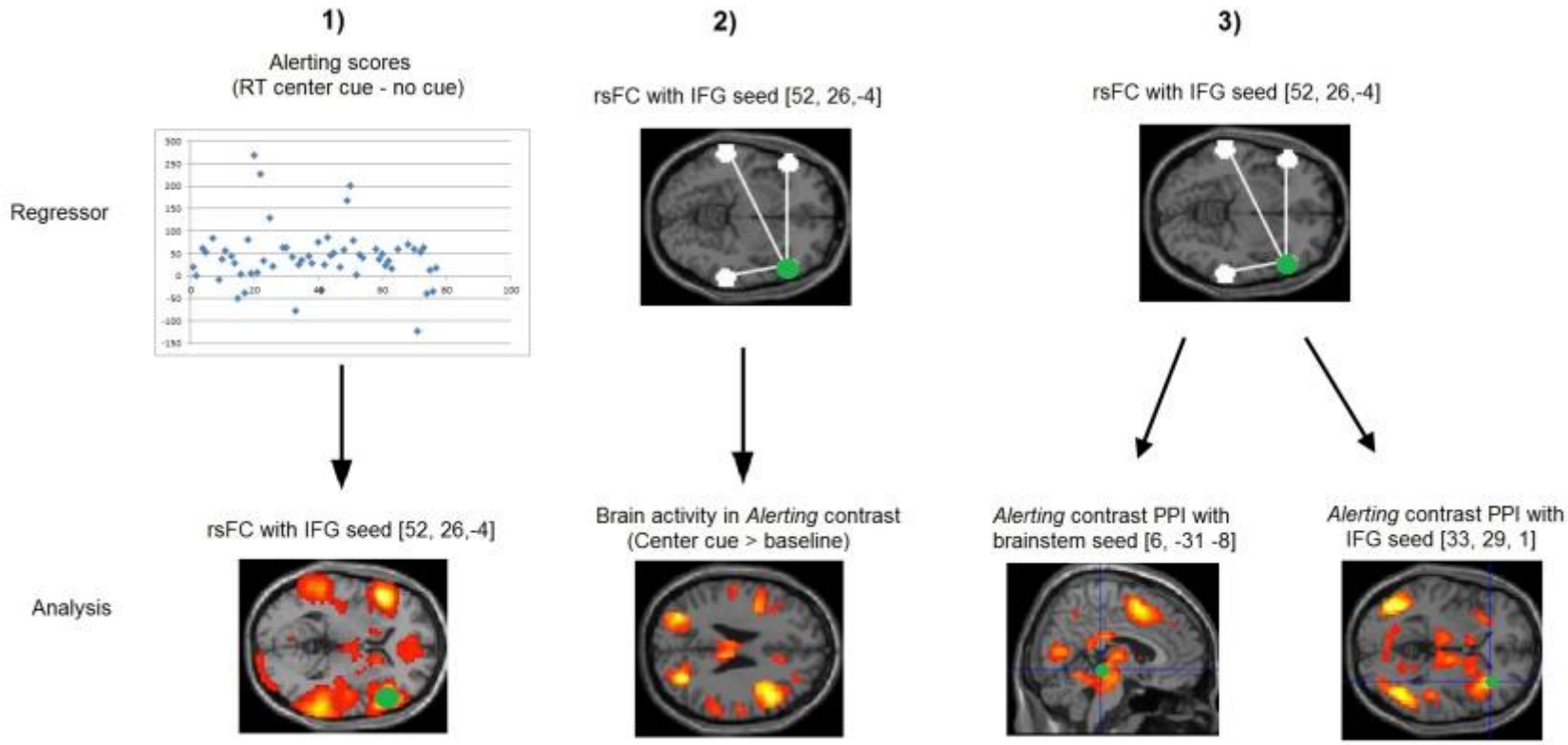


Figure 3.12. Schematic of methods used to test for correlation of resting-state functional connectivity with 1) alerting scores, 2) brain activity in the *Alerting* contrast and 3) brain connectivity on the ANT in the *Alerting* contrast.

ANT, attention network task; IFG, inferior frontal gyrus; rsFC, resting-state functional connectivity; PPI, psychophysiological interaction; RT, reaction time. Green spheres represent seed regions in resting-state and PPI analyses. 1) To test link between behavioral performance and rsFC, we entered alerting scores as regressors into the analysis of IFG seed rsFC. 2) To test link between ANT neural activity and rsFC, we extracted the connectivity between the IFG seed and the left IFG, left middle temporal gyrus, and right middle temporal gyrus, and entered these correlations simultaneously as regressors into the *Alerting* activation contrast. 3) To test link between ANT neural connectivity and rsFC, we entered rsFC of the IFG seed as regressors into the *Alerting* contrast PPI using brainstem and IFG seeds. PPI seeds were based on significant activation peaks from the same contrast.

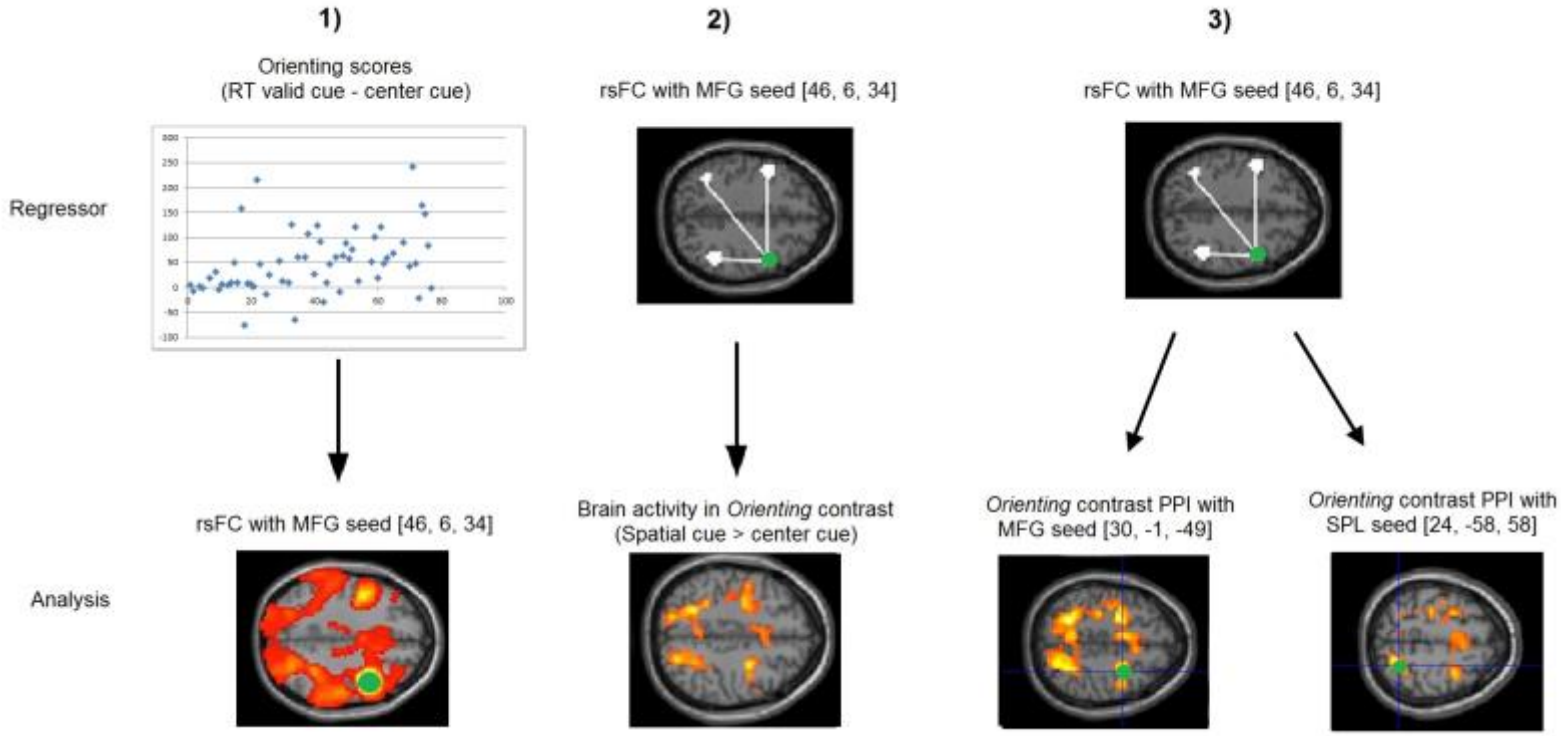


Figure 3.13. Schematic of methods used to test for correlation of resting-state functional connectivity with 1) orienting scores, 2) brain activity in the *Orienting* contrast and 3) brain connectivity on the ANT in the *Orienting* contrast.

ANT, attention network task; MFG, middle frontal gyrus; SPL, superior parietal lobule; rsFC, resting-state functional connectivity; PPI, psychophysiological interaction; RT, reaction time. Green spheres represent seed regions in resting-state and PPI analyses. 1) To test link between behavioral performance and rsFC, we entered orienting scores as regressors into the analysis of MFG seed rsFC. 2) To test link between ANT neural activity and rsFC, we extracted the connectivity between the MFG seed and the left MFG, left SPL, and right inferior parietal lobule, and entered these correlations simultaneously as regressors into the *Orienting* activation contrast. 3) To test link between ANT neural connectivity and rsFC, we entered rsFC of the IFG seed as regressors into the *Orienting* contrast PPI using MFG and SPL seeds. PPI seeds were based on significant activation peaks from the same contrast.

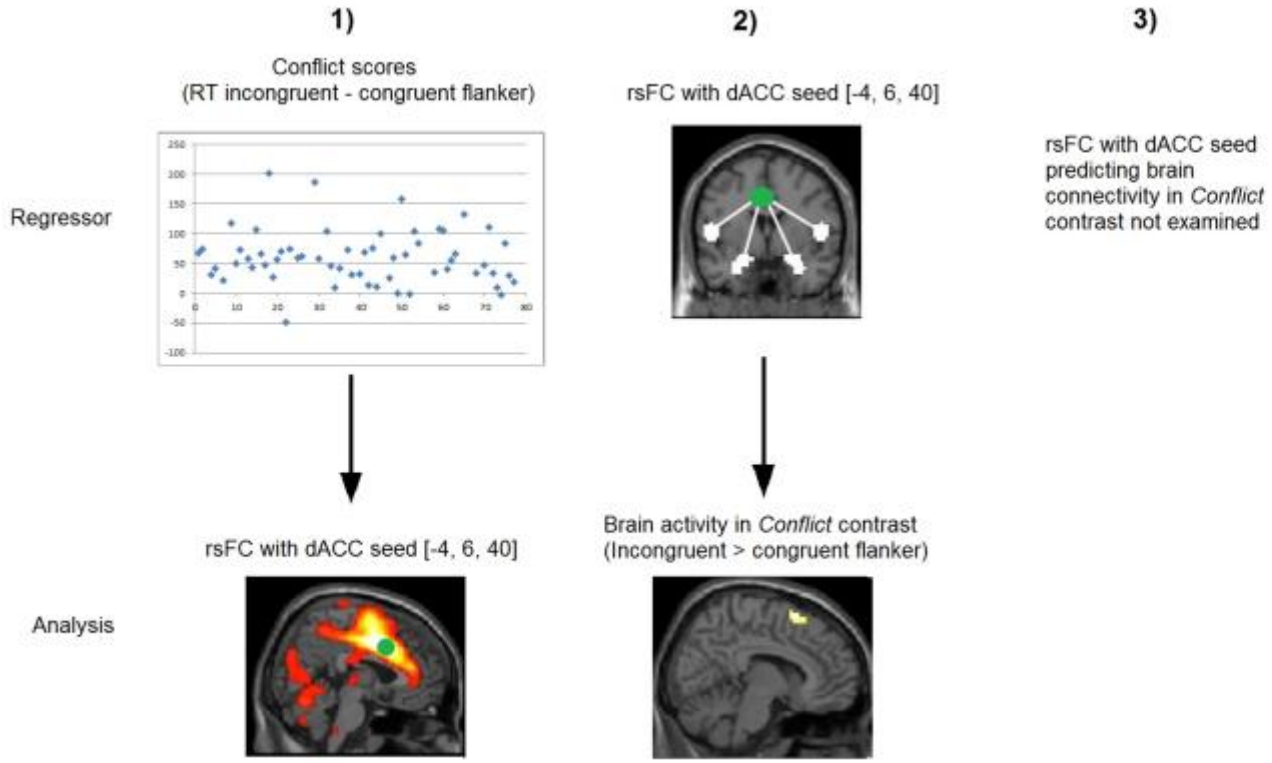


Figure 3.14. Schematic of methods used to test for correlation of resting-state functional connectivity with 1) conflict scores and 2) brain activity in the *Conflict* contrast.

ANT, attention network task; dACC, dorsal anterior cingulate cortex; rsFC, resting-state functional connectivity; PPI, psychophysiological interaction; RT, reaction time. Green spheres represent seed regions in resting-state and PPI analyses. 1) To test link between behavioral performance and rsFC, we entered conflict scores as regressors into the analysis of dACC seed rsFC. 2) To test link between ANT neural activity and rsFC, we extracted the connectivity between the dACC seed and the right insula, left insula, left amygdala and right amygdala. 3) We were not able to examine rsFC predictors of *Conflict* connectivity as there was no significant connectivity in this contrast.

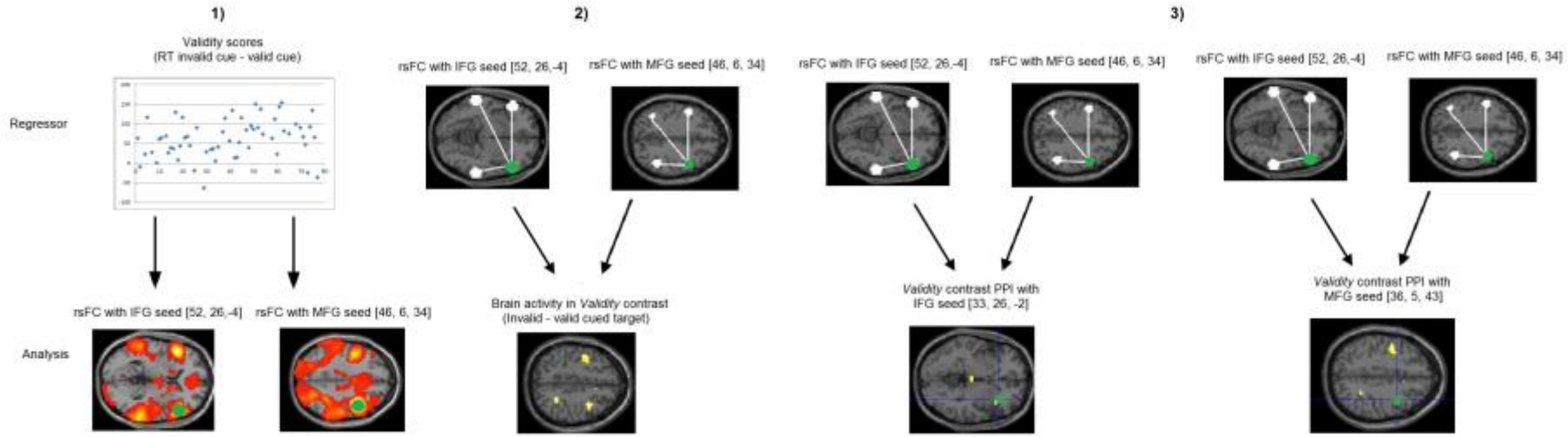


Figure 3.15. Schematic of methods used to test for correlation of resting-state functional connectivity with 1) validity scores, 2) brain activity in the *Validity* contrast and 3) brain connectivity on the ANT in the *Validity* contrast.

ANT, attention network task; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; rsFC, resting-state functional connectivity; PPI, psychophysiological interaction; RT, reaction time. Green spheres represent seed regions in resting-state and PPI analyses. 1) To test link between behavioral performance and rsFC, we entered disengagement scores as regressors into the analyses of IFG and MFG seed rsFC. 2) To test link between ANT neural activity and rsFC, we extracted the connectivity between the IFG seed and the left IFG, left middle temporal gyrus, and right middle temporal gyrus, and the connectivity between the MFG seed and the left MFG, left superior parietal lobule, and right inferior parietal lobule, and entered these correlations simultaneously as regressors into the *Validity* activation contrast. 3) To test link between ANT neural connectivity and rsFC, we entered rsFC of the IFG and MFG seeds as regressors into the *Validity* contrast PPI using IFG and MFG seeds. PPI seeds were based on significant activation peaks from the same contrast.

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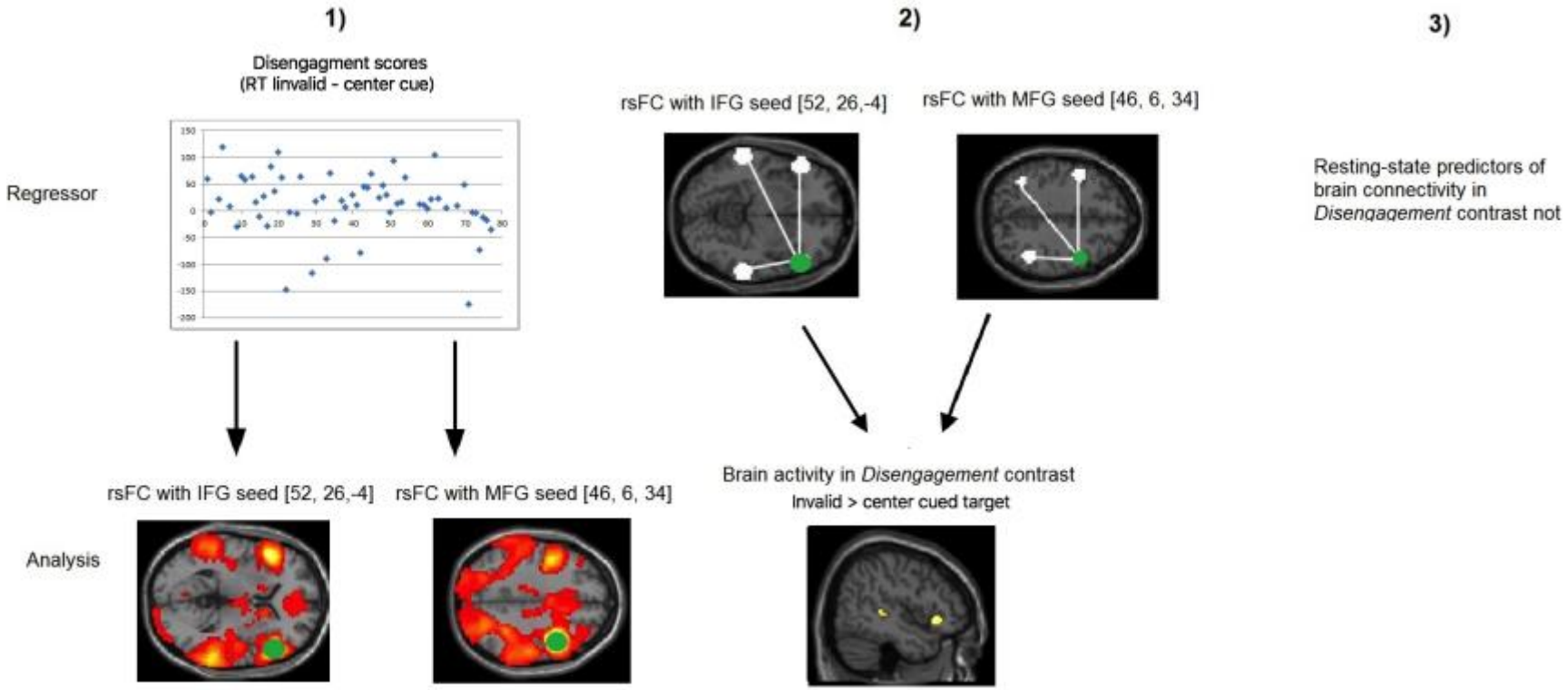

Figure 3.16. Schematic of methods used to test for correlation of resting-state functional connectivity with 1) disengagement scores and 2) brain activity in the *Disengagement* contrast.

ANT, attention network task; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; rsFC, resting-state functional connectivity; PPI, psychophysiological interaction; RT, reaction time. Green spheres represent seed regions in resting-state and PPI analyses. 1) To test link between behavioral performance and rsFC, we entered validity scores as regressors into the analyses of IFG and MFG seed rsFC. 2) To test link between ANT neural activity and rsFC, we extracted the connectivity between the IFG seed and the left IFG, left middle temporal gyrus, and right middle temporal gyrus, and the connectivity between the MFG seed and the left MFG, left superior parietal lobule and right inferior parietal lobule, and entered these correlations simultaneously as regressors into the *Disengagement* activation contrast. 3) We were not able to examine rsFC predictors of *Disengagement* connectivity as there was no significant connectivity in this contrast.

CHAPTER IV

Experiment 3: Neural Mechanisms of Attention Deficits in PTSD

Many independent lines of investigation have implicated attention abnormalities in PTSD. First and foremost, patients with PTSD describe symptoms of hyperarousal, concentration difficulties and intrusive thoughts (American Psychiatric Association, 2013; VanElzakker, 2016), all of which may be related to attention abnormalities. For example, PTSD patients frequently report lapses of attention, difficulty focusing and becoming distracted (Lew et al., 2011). Second, there is high comorbidity between PTSD and Attention Deficit Hyperactivity Disorder (ADHD) (Hahn et al., 2015). Third, PTSD patients display altered attention biases towards emotional stimuli (Pineles et al., 2009). Fourth, PTSD participants have altered performance on neuropsychological tests of attention (Aupperle et al., 2012; Polak et al., 2012; Qureshi et al., 2011).

A growing body of research has implicated aberrant resting-state functional connectivity (rsFC) in intrinsic connectivity networks (ICNs) which are thought to be related to attention in PTSD (Bluhm et al., 2009; Gong et al., 2014; Kennis et al., 2015, 2016; Lanius & Bluhm, 2010; Miller et al., 2017; Nicholson et al., 2016; Raji et al., 2015; Sripada, King, Garfinkel, et al., 2012; Yin et al., 2012). Salience network (SN) and default mode network (DMN) abnormalities have been most consistently reported in PTSD, suggesting that their functioning may be related to observed attention impairments. The findings from Experiment 1 and 2 showed that rsFC is predictive of attention task performance, neural activity and connectivity.

The findings of Experiment 1 also imply that the balance normally observed between ICNs at rest is disrupted in PTSD and this might be linked to attention deficits in this disorder. Although participants with PTSD exhibited greater cross-network connectivity of attention ICNs and larger orienting effects, there was not a significant across-subject correlation between these measures. Therefore, the mechanism underlying attention functioning in PTSD remains unclear. Several neuroimaging studies of inhibition - oddball (Bryant et al., 2005; Felmingham et al., 2009), Go-No/Go (Falconer et al., 2008; Stevens et al., 2016) and conflict (Bremner et al., 2004; Yennu et al., 2016) - in PTSD have reported decreased activation of the ventral attention network (VAN) and dorsal attention network (DAN), ICNs that are thought to be involved in alerting, orienting and disengagement. It is possible that during task performance, individuals with PTSD are unable to downregulate the SN and DMN. Furthermore, there have been no neuroimaging studies of specific orienting attention tasks in PTSD to investigate this issue. This was the goal of Experiment 3.

In Experiment 1, participants with PTSD exhibited altered performance in the orienting of attention, which we interpreted to be due to deficits in disengagement and utilization of spatial information, because participants with PTSD were slower to respond to targets that were preceded by non-spatial (center location) cues compared to controls. We were not able to directly measure disengagement in Experiment 1 because the original version of the Attention Network Test (ANT) does not include invalid cues. The modified version of the ANT that we established in Experiment 2 provides a more direct measurement of disengagement, by including invalid cues at a 20% contingency rate. In order words, on a subset of trials, spatial cues incorrectly inform the participant of the location of the upcoming targets, which requires the

disengagement and reorienting of attention to the opposite location in order to respond. Comparing the reaction time (RT) on invalid – valid cue trials provides a measurement of the entire orienting process, which can be further broken down into the comparisons of invalid – center cue trials (disengagement) and center – valid cue trials (moving and engaging).

Experiment 1 was also limited by the use of community rather than trauma exposed controls. Consistent with epidemiological studies (Kessler et al., 1995; Norris, 1992; Resnick, Kilpatrick, Dansky, Saunders, & Best, 1993), 50% of our control sample had experienced a traumatic event, including a motor vehicle accident, an armed robbery and having a terminally-ill child. While there were no significant differences in ANT performance between those who had experienced a traumatic event and those who had not, it is possible that our findings are partially related to trauma exposure. Many studies have found PTSD participants to have cognitive impairments (Hahn et al., 2015; Jenkins et al., 2010; Lagarde et al., 2010; Leskin & White, 2007; Pineles, Shipherd, Welch, & Yovel, 2007; Sumner et al., 2017; Sutker et al., 1995) and altered rsFC (Bluhm et al., 2009; Cao et al., 2008; Gong et al., 2014; Kennis et al., 2015, 2016; Lanius & Bluhm, 2010; Miller et al., 2007; Raji et al., 2015; Wu et al., 2011; Yin et al., 2012) even compared to trauma-exposed controls without PTSD. Studies on the neuropsychological function of those with trauma exposure but without PTSD have been mixed, with some studies reporting trauma-related impairment (Stein et al., 2002; Steudte-Schmiedgen et al., 2014) and others reporting no differences between trauma and non-trauma exposed controls (Jenkins et al., 2010; Lagarde et al., 2010; Leskin & White, 2007).

Hypotheses

In order to address these limitations and remaining questions, in Experiment 3 we aimed to determine the neural circuits associated with attentional impairments in PTSD by comparing PTSD participants to trauma and non-trauma exposed controls on the ANT (behavioral, neural activation and on-task connectivity) and rsFC.

3.1) Relative to both control groups, the PTSD group will show greater disengagement effects. Although Experiment 3 will be a cross-sectional study unable to determine causality, if we find there are no differences between trauma-exposed healthy controls and non-trauma exposed healthy controls on measures of attention, this will suggest that attention deficits in PTSD are not solely the result of trauma exposure. If instead we find there are differences between trauma and non-trauma exposed controls on measures of attention, this will suggest that attention deficits in PTSD may, to some extent, reflect trauma exposure or trauma severity.

3.2) Relative to both controls groups, the PTSD group will show decreased VAN and DAN activation during disengagement, but greater SN activation, as SN cross-network connectivity was related to attention performance in Experiment 1.

3.3) Relative to both control groups, the PTSD group will show greater cross-network connectivity at rest and on-task.

Methods

Participants. The participants were the same as those described in Experiment 2. A between-participants design was employed with three groups: PTSD (N=24), trauma-exposed controls (TEC; N=20) and non-trauma exposed controls (NTC; N=19). Analyses focused on the comparison of these three groups.

Measures. Participants completed the same measures (CAPS, MINI, Resting-state fMRI and ANT) as in Experiment 2.

Procedure. The procedure was the same as in Experiment 2.

Data analyses.

Demographics. A between sample t-tests were used to test for differences between the PTSD and TEC group in PTSD symptoms severity (CAPS). One-way ANOVAs were used to test for group differences in age and years of education. Chi-squared tests were used to test for group differences in gender, race, interpersonal trauma history, mTBI history and the number of people with medical conditions.

Part 1: ANT behavioral analysis and neural correlates. As in Experiment 2, runs with accuracy of less than 75% were excluded. RT outliers, defined as responses made after the designated response window (Xuan et al., 2016), were excluded if they were more than two standard deviations greater than the mean RT for the individual subject. There were no lower boundary RT outliers defined as responses that were less than 200 ms (Fan et al., 2007; Gamboz et al., 2010).

One-way ANOVAs were used to test for group differences in mean reaction time (RT), standard deviation (SD) of reaction time and accuracy across the whole task. Repeated measures ANOVAs were used to test for the effects of group (PTSD, TEC and NTC) and cue/flanker type on the five attention components (alerting, orienting, disengagement. validity and conflict). Pearson correlations were used to test for correlation of ANT scores with accuracy. Within the PTSD group, a between participants t-test was used to test for performance differences in those

taking and those not taking psychiatric medications. We also ran five ANCOVAS to test for group differences in ANT performance with mean RT as a covariate.

We then conducted a series of analyses to better understand any ANT components that emerged as significantly different between the groups (validity). First, we examined the correlation of ANT performance with PTSD symptoms severity on the CAPS in the PTSD group alone. To do this, we ran two regressions, the first with total CAPS scores predicting ANT performance, controlling for mean RT and the second with CAPS subscores predicting ANT performance controlling for mean RT.

Second, we examined brain activity during the contrast of interest which matched our behavioral difference (*Validity:* invalidly-validly cued targets; *Orienting:* spatial – center cues). Functional data was processed and analyzed using the same methods as in Experiment 2. To examine group differences in brain activation, contrasts maps were entered into second-level random effects analyses. Behaviorally, the comparisons of PTSD-NTC and TEC-NTC contributed to significance in a one-way ANOVA comparing the three groups. Thus, for the neural contrasts, we only examined these two comparisons as well. In the PTSD group, we also examined the correlation of PTSD symptom severity with brain activity. To this end, we entered total CAPS score as a regressor in the neural contrast. We then ran one regression with the four CAPS subscales in the neural contrast to determine the contribution of symptom clusters on the previous findings. Findings were small volume corrected within 10-mm spheres created from the peaks of significant findings in the total CAPS analysis. Additionally, we sought to determine the neural correlates of the behavioral group differences that we observed in the magnitude of the validity effect. To this end, we examined the interaction of group and the

behavioral validity effect in a generalized linear model of the neural *Validity* and *Orienting* (spatial – center cue) contrasts. Post-hoc analyses were conducted within each group separately to determine directionality. Findings were corrected for multiple comparisons using a family-wise error (FWE) correction of a $p < 0.05$ across the entire brain with a voxelwise threshold of $p < 0.005$ uncorrected.

Third, we examined brain connectivity during the contrast of interest which matched our behavioral difference. To evaluate the functional connectivity during the ANT, we utilized a PPI analysis as described in Experiment 2. Resulting contrast maps were entered into second-level random effects analyses to compare group differences in on-task connectivity. Furthermore, in the PTSD group, we examined the correlation of PTSD symptom severity with connectivity during ANT contrast of interest. To this end, we entered total CAPS score as a regressor in the PPI contrast of interest. Next, we examined the interaction of group and the behavioral ANT effect in a generalized linear model of the PPI contrast. Post-hoc analyses were conducted within each group separately to determine directionality. Findings were corrected for multiple comparisons using a FWE correction of a $p < 0.05$ across the entire brain with a voxelwise threshold of $p < 0.005$ uncorrected.

Fourth, we examined the correlation of all ANT components with group differences behaviorally with resting-state functional connectivity. Resting-state data was processed and analyzed using the same methods as Experiment 2. In short, we used a seed-based approach to examine connectivity of the VAN, DAN, SN and DMN using IFG, MFG, dACC and PCC seeds, respectively. We entered the behavioral ANT effect as a regressor into each resting-state analysis for a total of four generalized linear models. We then examined the interaction of group

and the behavioral ANT effect for each model. Post-hoc analyses were conducted within each group separately to determine directionality. Findings were corrected for multiple comparisons using a FWE correction of a $p < 0.05$ across the entire brain with a voxelwise threshold of $p < 0.005$ uncorrected.

Part 2: Resting-state functional connectivity. Because abnormalities in resting-state functional connectivity (independent of task performance) have been reported in PTSD, we also conducted a series of analyses to determine if we could replicate these results. To this end, we entered z-score images from the IFG, MFG, dACC and PCC seeds into four one-way ANOVAs to determine differences in connectivity amongst the three groups. Findings were small volume corrected within an ICN search mask (same as Experiment 1 based on (De Luca et al., 2006)) using an FWE correction at the cluster level with a voxelwise threshold of $p < 0.005$ uncorrected. Post-hoc tests were conducted in each group separately to determine the contribution of each group to the ANOVA findings. 10-mm ROIs centered on the peak coordinates from significant ANOVA results were used as small volume masks in the analyses of each group separately.

We also entered total CAPS scores as a regressor into the connectivity analysis of each seed, followed by regressions using CAPS subscores to examine whether connectivity was associated with PTSD severity. Findings were small volume corrected within the same ICN search masks using a FWE correction at the cluster level with a voxelwise threshold of $p < 0.005$ uncorrected.

We next sought to test if rsFC differences found in the above analyses were predictive of task performance, activation or connectivity on the ANT. To test for correlations with task performance, we extracted the average time-series from 10-mm spheres centered around the peak

coordinates of each finding. We conducted Pearson correlations with the extracted time-series and ANT behavioral performance. We only examined correlations with behavioral effects that were hypothesized to involve the resting-state seed from which the finding emerged. For example, for rsFC differences that were found with the dACC seed, we only examined the correlation with the ANT conflict effect. To test if these rsFC differences were predictive of task performance, we entered the extracted time series into the ANT contrast of interest. Similarly, rsFC differences that were found with the dACC seed were only examined for prediction in the *Conflict contrast*, because of the hypothesized role of this network in conflict (Botvinick et al., 2004). Lastly, to test if these rsFC differences were predictive of task connectivity, we entered the extracted resting-state time series into the PPI contrasts of interest (e.g. rsFC differences from the IFG seed were examined only in the alerting, validity and disengagement contrasts and they are hypothesized to involve the VAN (Vossel et al., 2014)). Findings were corrected for multiple comparisons using a FWE correction of a $p < 0.05$ across the entire brain with a voxelwise threshold of $p < 0.005$ uncorrected.

Part 3: Exploratory analyses. To better understand attention functioning in PTSD, we examined group differences in brain activation and connectivity during the *Alerting, Conflict* and *Disengagement contrasts*, despite not finding significant group differences behaviorally. To this end, we conducted one-way ANOVAs to test for group differences in brain activity and connectivity during these three contrasts. For each ANOVA, we examined the findings using three search masks: the main effect of the task contrast (*Alerting, Conflict* or *Disengagement* main effect at $p < 0.005$ uncorrected), the mask of the SN used in Experiment 1 and the mask of the DMN used in Experiment 1. Results were small volume corrected within these search masks

using a FWE correction at the cluster level with a voxelwise threshold of $p < 0.005$ uncorrected. These search masks were chosen to examine differences in attention regions that are normally activated in the task and because of our specific hypotheses regarding the SN and DMN in PTSD. Post-hoc tests were conducted between each group pairwise to determine the contribution of each group to the ANOVA findings. 10-mm ROIs centered on the peak coordinates from significant ANOVA results were used as small volume masks in the post-hoc analyses.

Lastly, to test the link between behavioral ANT scores and PTSD severity, we conducted three sets of regressions to determine if PTSD severity on the CAPS would predict ANT scores behaviorally, controlling for mean RT (CAPS subscales x three ANT effects – alerting, conflict and disengagement). Findings were Bonferroni corrected for multiple comparisons.

Results

Demographics.

Demographics are reported in Table 3.1. As expected, the PTSD group reported significantly higher PTSD symptoms than the TEC group, $t(42) = 15.335$, $p < 0.001$. There were no significant group differences in age, years of education, or history of mTBI. Additionally, there were no differences in the number of people reporting comorbid medical conditions, however, the conditions differed qualitatively. In the PTSD group, medical conditions included interstitial cystitis, endometriosis, migraines, irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, spina bifida (corrected with surgery; no damage to central nervous system), sleep apnea, hypothyroidism (corrected with medication) and asthma. In the TEC group, medical conditions reported included acid reflux disease, nerve damage to foot, dysmenorrhea,

blood clotting disorder, hirsutism, bursitis and allergies. In the NTC group, reported medical conditions included polycystic ovary syndrome, anterior cruciate ligament injury and allergies. Fourty-two percent of the PTSD group was taking psychiatric medications (Fluoxetine, Buproprion, Escitalopram, Sertaline, Citalopram and Buspirone). There were no group differences in the usage of non-psychiatric medications. Medications in the PTSD group included Warfarin, birth control, Zyrtec, Singulair, Neurontin, Membic, Flexeril, Prazosin and Synthroid. Medications in the TEC group included birth control, Zyrtec, Warfarin, Spironolactone and Nasacort. Medications in the NTC group included birth control, Singulair, steroid eye drops and Minocycline for acne. Lastly, there was a significant difference between the PTSD and TEC groups in the type of trauma experienced, with a greater proportion of those in the PTSD group reporting interpersonal trauma than those in the TEC group.

Part 1. ANT behavior and neural correlates.

Mean RT, SD and accuracy. There were no significant group differences in mean RT, $F(1,57) = 0.177$, $p = 0.68$, standard deviation of RT, $F(1,57) = 0.014$, $p = 0.91$, percent accuracy $F(1,57) = 1.864$, $p = 0.18$, commission errors, $F(1,57) = 0.546$, $p = 0.46$, omission errors, $F(1,57) = 0.979$, $p = 0.33$, or RT outlier trials, $F(1, 57) = 2.063$, $p = 0.16$.

ANT components. One-way ANOVAs showed a significant group difference in the validity effect, $F(2,57) = 4.8915$, $p = 0.03$, but no significant difference in the other ANT components: Alerting, $F(2,57) = 0.008$, $p = 0.93$; Orienting, $F(1,57) = 2.105$, $p = 0.15$; Conflict, $F(2,57) = 1.478$, $p = 0.23$; Disengagement, $F(2,57) = 0.486$, $p = 0.49$ (see Figure 4.1). Post-hoc tests revealed that the PTSD group had a significantly smaller validity effect ($M = 68.77$, $SD = 42.54$) compared to the NTC group ($M = 97.31$, $SD = 39.70$), $t(38) = -2.188$, $p = 0.03$, which

was contrary to our hypothesis. There was no significant difference between the TEC group (M = 73.45, SD = 38.76) and the PTSD group, p = 0.72, but there was a marginally significant difference between the TEC and NTC groups, $t(36) = -1.875$, p = 0.07. One NTC subject was considered an outlier for validity due to having a score greater than 2SD of the sample mean. When this subject was excluded, the difference between the NTC and PTSD groups became marginal, p = 0.06 and difference between the NTC and TEC groups became non-significant, p = 0.12. Three individuals in the PTSD group were considered subthreshold, because they did not endorse full DSM-V criteria for PTSD. When these individuals were excluded, there remained a difference between the PTSD and NTC group, but the effect became marginal, p = 0.07. There was no significant different in the magnitude of the validity effect between those taking psychiatric medications and those who were not, $t(19) = 0.688$, p = 0.66.

The magnitude of the validity effect was significantly related to accuracy on the task as whole. In all participants, the validity effect was positively correlated with percent accuracy, $r(57) = 0.34$, p = 0.004, driven by a negative correlation with percent omission errors, $r(57) = -0.33$, p = 0.01. It was not correlated with percent commission errors, p = 0.22. Furthermore, when examining the groups independently, the relationship with omission errors was only present in the PTSD ($r(19) = -0.43$, p = 0.05) and TEC groups ($r(17) = -0.42$, p = 0.07), but not the NTC group ($r(17) = -0.11$, p = 0.64), however, the relationship in the PTSD group was not significant after removal of one outlier.

Because the validity effect is defined as the difference in RT between valid and invalid trials, follow-up t-tests were conducted comparing each group on the mean RT in these conditions. There were no significant group differences in RT on valid cue trials, p = 0.84, or

invalid cue trials, $p = 0.41$. One PTSD subject and one NTC subject were outliers for these conditions, having a mean RT greater than 2 SD that of the group mean. When removing these outliers, effects were still not significant.

Controlling for mean RT. Because mean RT on the task as a whole has been shown to affect ANT scores (Macleod et al., 2010), we repeated the between participants comparisons for the validity effect, valid cue RT and invalid cue RT (see Figure 4.2). When controlling for mean RT, there remained a significant group difference in the validity effect, $F(2,56) = 4.628$, $p = 0.04$, which was driven by a difference in the PTSD group compared to the NTC group, $p = 0.04$ and a marginal difference between the TEC and NTC groups, $p = 0.09$. Next, ANCOVAs were conducted to test group differences in the valid cue and invalid cue RTs, controlling for mean RT. When the two outlier participants were removed, the PTSD group was significantly slower in the valid cue trials compared to the NTC group, $F(1,37) = 6.34$, $p = 0.02$, but significantly faster in the invalid cue trials, $F(1,37) = 4.216$, $p < 0.05$. The TEC group was marginally faster in the valid cue condition compared to the NTC group, $F(1,34) = 3.569$, $p = 0.07$, but not different in the invalid cue condition, $F(1,34) = 2.267$, $p = 0.11$.

Correlates of spatial cue utilization.

PTSD symptom severity. There was not a significant correlation between validity scores and total CAPS scores, $r(18) = -0.03$, $p = 0.90$.

ANT task activation.

As stated in Experiment 2, five participants had runs that were excluded due to head movement (1 PTSD subject – all runs, 1 PTSD subject – 2 runs, 1 PTSD subject – 1 run, 1 TEC subject – 1 run). There were no differences in head movement for the remaining participants

(max space: $F(2,54) = 0.465$, $p = 0.63$; max angle: $F(2,54) = 0.583$, $p = 0.56$). Additionally, 1 TEC subject was excluded due to a chemical shift artifact.

Because of the group differences observed in the validity effect, we examined brain activity for the *Validity* (invalidly cued targets – validly cued targets) and the *Orienting* (spatial cue – center cue) contrasts. The validity effect behaviorally reflects the comparison of the psychological processes of disengaging spatial attention from an invalid location and orienting spatial attention to a valid location. We examined brain activity during the *Orienting* contrast, because orienting is a psychological process that is part of the validity effect. This allowed us to measure brain activity specific to viewing spatial cues (*Orienting*) and to processing spatially cued targets *Validity*). We found that there were no significant group differences in activation patterns on the *Orienting* or *Validity* contrasts. In the PTSD group alone, total CAPS scores were positively correlated with activation in the left putamen/insula for *Orienting* (see Table 4.1, Figure 4.3). This activity was positively correlated with intrusive and negative mood/cognitive symptoms. In the *Validity* contrast, total CAPS scores were positively correlated with activity in the right putamen, mPFC extending to the dACC and the PCC (see Table 4.1). Right putamen activity was positively correlated with intrusive and negative mood and cognitive symptoms at trend level, while PCC activity was positively correlated with negative mood and cognitive symptoms at a trend level. Additionally, hyperarousal symptoms were significantly correlated with left caudate activity at a whole brain level. In sum, greater PTSD severity was linked to greater SN and DMN activity during the *Orienting* and *Validity*, respectively.

We next sought to determine the neural correlates of the behavioral group differences that we observed in the magnitude of the validity effect. To this end, we examined the interaction of

group and the behavioral validity effect in a generalized linear model of the neural *Orienting* (spatial – center cue) and *Validity* (invalid target – valid target) contrasts. Because the smaller validity effects that were observed in the PTSD group reflected decreased utilization of all spatial information, we wanted to determine if this behavioral difference arose from differential brain activity during the processing of spatial cues (the neural *Orienting* contrast), during the process of responding to invalid targets compared to valid targets (the neural *Validity* contrast) or both. In the *Orienting contrast*, we found a significant group x behavior interaction in the right insula ([39, 2, 7], $k = 142$, $z = 3.56$, $p = 0.013$ FWE). In the PTSD group, smaller validity scores were correlated with more right insula activity ([39, 2, 7], $k = 9$, $z = 3.03$, $p = 0.064$ SVC), but in the NTC group, larger scores were correlated with more right insula activity ([42, 11, 10], $k = 4$, $z = 2.93$, $p = 0.104$ SVC). For the *Validity* contrast, we found significant group x behavior interactions in three areas: 1) the paracentral lobule extending to the precuneus, SMA, medial frontal gyrus and postcentral gyri, 2) the right MFG extending to the ACC, inferior operculum and superior frontal gyrus and 3) the right fusiform extending to the parahippocampal gyrus and cerebellum (see Table 4.2, Figure 4.4). Post-hoc tests showed that the validity effect was positively correlated with brain activity in these clusters in the PTSD group, but negatively correlated with these areas in the NTC group. In sum, decreased utilization of spatial cues in PTSD was linked with greater SN activity during the cue period and greater DAN and SN activity during the target period.

ANT connectivity.

We examined brain connectivity for the *Orienting* and *Validity* contrasts using seeds in the right MFG and right superior parietal lobule (SPL) (*Orienting*) and the right IFG and MFG

(*Validity*). Connectivity of these seeds was not significantly different between groups. For *Orienting*, total CAPS scores positively correlated with connectivity with the MFG seed and a) the bilateral cerebellum, b) the right angular gyrus and c) the superior medial frontal gyrus (see Table 4.3, Figure 4.3). Total CAPS scores were negatively correlated with connectivity between the right SPL seed and regions activated in the *Orienting* contrast including a) the precuneus, and b) the bilateral putamen, although the latter did not survive correction for multiple comparisons. Total CAPS scores did not correlate with connectivity in the *Validity* contrast. In sum, greater PTSD severity was linked with greater DAN-DMN connectivity, while decreased PTSD severity was linked with greater DAN-DAN connectivity.

To examine the link between validity score behavioral performance and brain connectivity, we next examined the interaction of group x validity scores in 1) the PPI for the *Orienting* contrast with the MFG seed, 2) the PPI for the *Orienting* contrast with the SPL seed, 3) the PPI for the *Validity* contrast with the IFG seed and 4) the PPI for the *Validity* contrast with the MFG seed. For *Orienting*, there was a significant group (NTC and TEC) x validity score interaction of the right MFG seed with a) right inferior parietal lobule (IPL) extending to the IFG, MFG, precuneus, precentral gyrus, supramarginal gyrus, SPL, angular gyrus, MTG, caudate and superior occipital gryus, b) the right superior temporal gyrus (STG)/putamen, c) the midbrain/thalamus, d) the cerebellum/parahippocampus, d) the right STG/insula, e) the left precentral gryus and f) the mPFC (see Table 4.4, Figure 4.5). Post-hoc tests of the correlation of validity scores within individual groups showed that only 1 region (the MFG – left orbital frontal cortex connectivity) was correlated with validity scores in NTC group. There were, however, significant positive and negative correlations in the TEC group. In the TEC group, greater

connectivity of the MFG with a) the right midbrain/parahippocampus/cerebellum, b) the right STG/insula, c) the mid-cingulate/SMA, d) the left precentral gyrus/IPL, e) the left fusiform/hippocampus and f) the right MFG was associated with larger validity scores. In contrast, greater connectivity of the MFG with a) the right amygdala extending to the STG, putamen, midbrain and hippocampus, b) the R IPL extending to the IFG, MFG, insula, supramarginal gyrus, angular gyrus, SPL and mid-cingulate and C) the right superior frontal gyrus was associated with larger validity scores.

In the *Orienting* contrast, there was also a significant group (NTC and TEC) x validity score interaction of the right SPL seed with a) a large cluster encompassing the bilateral PFC, left insula, left putamen and left hippocampus, b) a more posterior cluster encompassing the bilateral temporal lobe, PCC, precuneus, middle occipital gyrus, right caudate, left angular gyrus, right insula and right amygdala and c) the left precuneus/paracentral lobule (see Table 4.5). Post-hoc tests of the correlation of validity scores within individual groups showed that none of these regions were correlated with connectivity in the NTC group. There were, however, significant positive and negative correlations in TEC group. In the TEC group, greater connectivity of the SPL with all the above regions, except for the right precentral gyrus, was associated with larger validity scores. In contrast, greater connectivity of the SPL with the right precentral gyrus was associated with smaller validity scores. Thus, in trauma-exposed controls, greater focused attention to spatial cues was linked to greater DAN connectivity across multiple neural networks (SN, DMN, VAN and DAN), while less focused attention to spatial cues was associated with greater DAN-SN connectivity.

In the *Validity* contrast, we found that there were significant group (PTSD and NTC) x validity score interaction of the IFG seed with a) the medial frontal gyrus, b) left middle temporal gyrus, c) right superior/middle temporal gyrus, d) paracentral lobule, e) right IFG, f) right MFG and g) left SPL (see Table 4.6, Figure 4.6). Additionally, we found that there were significant group (TEC and NTC) x validity score interactions of the IFG seed with a) the left angular gyrus, b) precuneus, c) medial and superior frontal gyrus, d) left precentral gyrus, e) right postcentral gyrus, f) left insula, g) left IPL and h) right MFG. Post-hoc tests of the correlation of validity scores within individual groups, showed that none of these regions were correlated with connectivity in the NTC group. There were, however, significant positive and negative correlations in the PTSD and TEC groups. In the PTSD group, greater connectivity of the IFG with a) the bilateral superior and middle temporal gyri and b) the bilateral MFG was associated with larger validity scores. In the PTSD group, greater connectivity of the IFG with a) the precuneus/PCC, b) the medial frontal gyrus, c) the left putamen and d) the SMA/mid cingulate cortex was associated with smaller validity scores. In the TEC group, greater connectivity of the IFG with a) the bilateral insula, b) left superior parietal lobe, c) right putamen, d) right postcentral gyrus extending to the IPL and e) the right MFG was associated with larger validity scores. In contrast, greater connectivity of the IFG with a) bilateral angular gyri, b) medial and superior frontal gyrus and c) left MFG extending to the inferior orbital gyrus was associated with smaller validity scores in the TEC group. There were no significant group x validity score interactions with the MFG seed. Thus, in trauma-exposed controls, decreased utilization of spatial information behaviorally was linked to greater VAN-DMN connectivity in

the *Validity* contrast, but increased utilization of spatial information was linked to with greater VAN connectivity with attention control, motor and sensory regions in the *Validity* contrast.

Resting-state connectivity.

We examined group differences in the correlation of resting-state functional connectivity and behavioral validity scores (see Table 4.7). For the VAN, we found that there was a significant group (PTSD and NTC) x validity score interaction of the IFG seed with the left IFG. As we reported in Experiment 1, the left IFG was associated with larger validity scores in the NTC group. In the PTSD group, there was a negative, but non-significant relationship of connectivity with validity scores. For the DAN, there was a significant group (PTSD and NTC) x validity score interaction of the MFG seed with the right MTG. Tests within individual groups showed that there was no relationship of this area with behavioral performance in the NTC group, but a significantly negative relationship in the PTSD group, such that greater connectivity was related to faster performance in valid cue trials. For the DMN, there was a trend level group (PTSD and NTC) x validity score interaction of the PCC seed with the left MFG, however post-hoc tests showed that this area was not significant in either group alone. Lastly, for the SN, there was no significant group x validity score interaction of the dACC seed.

Part 2. Resting-state connectivity independent of task performance.

Independent of task performance, one-way ANOVAs showed that there were no group differences in rsFC with the IFG, MFG or PCC seeds. There was a significant group difference of dACC connectivity with a parietal white matter bundle just dorsal to the left ventricle, which was outside of the search masks ([-24 -46 22], k = 30, z = 4.99, $p = 0.024$ whole brain FWE, see Figure 4.7). These areas were positively connected in the NTC group ([-24 -46 22], k = 5.30, $p =$

0.015 SVC), but were not connected in the PTSD or TEC groups. We did not test if connectivity between these regions predicted ANT measures, as the cluster did not include gray matter.

In the PTSD group alone, dACC – left cerebellar/midbrain connectivity ([-6 -22 -23], k = 144, z = 3.45 p = 0.012 FWE) was negatively correlated with total CAPS scores, but was not related to CAPS subscales. This connectivity was not correlated with the behavioral conflict effect. This connectivity was not predictive of neural activation during the conflict contrast. Connectivity during the conflict contrast was not examined as the PPI yielded no significant results with the seed chosen (see Experiment 2).

Additionally, in the PTSD group alone right IFG – left postcentral gyrus connectivity was positively correlated with total CAPS scores, but not with CAPS subscales. Connectivity between these regions was not correlated with alerting, validity or disengagement scores, all of which are types of attention which involve the IFG. Greater connectivity between these regions, however, predicted greater right putamen/caudate/insula activity ([24 -7 10], k = 166, z = 3.86, p = 0.017 FWE) during the validity contrast and decreased left insula/precentral gyrus/IFG/superior temporal gyrus activity [-57 8 13], k = 146, z = 4.07, p = 0.012 FWE) during the disengagement contrast. Resting-state connectivity between the right IFG and left postcentral gyrus did not predict on-task connectivity.

Part 3. Exploratory analyses

PTSD severity. Hyperarousal symptoms were negatively correlated with orienting scores, B = 9.91, p = 0.04, driven by faster RT on center cue trials, B = 11.2, p = 0.008, but were not significant after removing one outlier. Symptoms on the CAPS were not correlated with any other ANT effects.

ANT activation. One-way ANOVAs revealed that there were significant group differences in brain activity during the *Conflict* contrast (see Table 4.8, Figure 4.8). There was no main effect of group on brain activity during the *Alerting* or *Disengagement* contrasts. During conflict, there was a significant main effect of group in the right and left insula and ACC. Post-hoc t-tests showed that both the PTSD and TEC groups had greater right insula activity compared to the NTC group, while the TEC group had significantly greater activity in the left insula and ACC compared to both the PTSD and NTC groups. In the PTSD group alone, right insula activity was positively correlated with total CAPS scores, $r(17) = 0.41$, $p = 0.04$. There were no significant results for the PTSD>TEC or NTC>TEC comparisons.

ANT connectivity. There were no significant group differences in connectivity during the ANT.

Discussion

Separate lines of research have implicated attention abnormalities in PTSD using multiple methodologies (behavioral, neural activation and functional connectivity), but few studies have combined these approaches. Each of these methods can provide important information about PTSD; however, the interpretation is limited unless each method is combined with the other approaches, thereby providing a more enriched understanding of underlying pathophysiology. Experiment 3 aimed to determine the neural mechanisms of attentional impairments in PTSD by examining resting-state functional connectivity, behavioral performance and neural activation and connectivity during the attention network task. Achieving this aim could contribute to our understanding of the neurobiological basis of PTSD-related attentional abnormalities. We had four main findings. First, the PTSD group showed deficits in

the utilization of spatial information. Second, the PTSD group showed both intrusion of the SN and DMN during task performance, as well as increased engagement of the VAN and DAN. Third, the TEC group exhibited results more similar to those of the PTSD group than to those of the NTC group. Fourth, the PTSD group did not exhibit differences in resting-state functional connectivity of intrinsic connectivity networks.

PTSD deficits in utilization of spatial information.

Compared to non-trauma controls, participants with PTSD showed smaller validity scores on the ANT, driven by both slower RT to validly cued targets and faster RT to invalidly cued targets. As such, cue information did not appear to help or hinder performance in the PTSD group as much as it did in healthy controls. This is consistent with Experiment 1, where we reported that PTSD participants were slower to respond to spatially cued targets, which was further modulated by PTSD severity. This is also consistent with the neuropsychological literature that has consistently implicated orienting attention deficits in PTSD (Brandes et al., 2002; Hart et al., 2008; Jenkins et al., 2010; Koenen et al., 2001; Koso & Hansen, 2006; Lagarde et al., 2010; Madu & Peltzer, 2000; Parslow & Jorm, 2007; Polak et al., 2012; Stein et al., 2002; Sutker et al., 1995). Contrary to our hypothesis, however, we did not find behavioral evidence of disengagement difficulties in PTSD as we did in Experiment 1, which is inconsistent with prior reports of disengagement deficits in PTSD (Bardeen, Tull, Daniel, Evenden, & Stevens, 2016; El Khoury-Malhame et al., 2011; Pineles et al., 2009, 2007).

There are several potential explanations for the differences in our findings compared to previous studies. First, disengagement difficulties may be specific to trauma stimuli. Studies that have reported disengagement difficulties in PTSD have either been specific to threatening

stimuli, or have included PTSD participants as part of a larger sample of anxiety disorder patients (Pacheco-Unguetti et al., 2011), thus making it unknown if the finding was driven by other anxiety disorders in the latter case. Only two other studies have utilized the ANT in PTSD – one reported deficits in conflict monitoring (Leskin & White, 2007) and the other reporting deficits in orienting (Barlow-Ogden & Poynter, 2012), but neither study used a version which included invalid cues. Thus, this is the only study we are aware of that directly tested disengagement of attention to non-affective stimuli in PTSD.

Second, the version of the ANT that we used in this study differed from that of Experiment 1, because we included invalid cues. Across both studies, we found evidence for deficits in orienting attention, but only in Experiment 1 did we find evidence for disengagment deficits. In experiment 1, all cues were 100% predictive of the appearance of targets either temporally or spatially. In this version, none of the cues were 100% predictive. Spatial cues were 70% predictive and even temporal cues were only 79% predictive because we included cue only trials to better separate cue and target related brain activity. It is possible that there would have been increased attentional capture with if the cues were more predictive. This is consistent with (Vossel et al., 2006), who reported that increasing the predictability of spatial cues resulted in larger validity effects and greater VAN activity during an orienting task. It is possible that PTSD participants employ different strategies to complete the task depending on the "usefulness" of the information. A future study could examine how varying the proportion of valid – invalid trials affects disengagement in PTSD.

Finally, the demographics of Experiment 1 and 3 were very different. The sample in Experiment 1 consisted of all male veterans seeking PTSD treatment at the VA, whereas the

sample in Experiment 3 consisted of mostly female, non-treatment seeking, community members. Thus, differences in gender, functional impairment and trauma type could account for the discrepancies in our findings. Additionally, in Experiment 1, there was a higher percentage of people in the PTSD group taking psychiatric medications and who had experienced an mTBI. Some studies have reported that antidepressant use is associated with cognitive impairment (Amado-Boccara, Gougoulis, Poirier Littré, Galinowski, & Lôo, 1995; Nagane et al., 2014), however, other studies have also reported improved cognitive functioning in patients with major depression following antidepressant treatment (Castellano et al., 2016; McIntyre, Harrison, Loft, Jacobson, & Olsen, 2016). We did not find any differences in ANT performance between those who were taking psychiatric medications and those who were not, so we do not believe that this alone could account for the differences in our findings. Mild TBI has also been associated with cognitive deficits (Miotto et al., 2010), but in Experiment 1, mTBI was associated with decreased utilization of spatial cue information, consistent with our results here, not disengagement deficits. Thus, that also is not likely to account for differences in findings.

Our findings may support a novel model of PTSD, which postulates deficits in contextual processing underlie the disorder (Liberzon & Abelson, 2016). According to this theory, individuals with PTSD fail to use environmental or background information appropriately to guide their behavior. Such environmental information is critical in helping us distinguish a lion in the wild from a lion in the zoo. This could explain why individuals with PTSD show abnormal fear responses in both safe and threatening environments (Jovanovic, Kazama, Bachevalier, & Davis, 2012; Rougemont-Bücking et al., 2011). Recently, van Rooij, Geuze, Kennis, Rademaker, and Vink (2014) reported that PTSD participants showed deficits in the

utilization of a contextual warning cue on a stop signal task, showing that such impairments in using contextual information may not be limited to affective states. This is consistent with our findings that PTSD participants did not appropriately use non-affective spatial cues to inform them of the location of upcoming targets. As discussed below, several biological mechanisms may underlie this deficit.

Salience network intrusions during spatial cue processing in PTSD.

We hypothesized that the PTSD group would show SN intrusions upon the DAN and VAN during disengagement. Our results partially supported this hypothesis. While we did not find greater activation of the SN during the processing of invalidly cued targets, we did find altered SN activation and connectivity during the processing of spatial cues. Specifically, greater PTSD severity was associated with greater left insula activation and decreased utilization of spatial information (smaller validity scores) was associated with greater right insula activity. Additionally, greater PTSD severity was associated with greater left amygdala activity during the processing of spatial cues and the PTSD group had greater connectivity of the DAN with several SN regions (bilateral amygdala, ACC, left insula) compared to the NTC group during the processing of spatial cues, but these findings were not significant after correction for multiple comparisons. Importantly though, these regions have not been shown to be involved in spatial orienting (Fan et al., 2005) and did not show positive activation during the orienting condition in all participants. These findings are consistent with the literature implicating hyperactivity of SN regions in PTSD (Duval, Javanbakht, & Liberzon, 2015) and alerted SN connectivity at rest (Daniels et al., 2010; Sripada, King, Garfinkel, et al., 2012; Sripada, King, Welsh, et al., 2012). The SN is involved in detecting salient and personally relevant stimuli (Menon & Uddin, 2010).

Greater recruitment of the insula during the processing of spatial cues could reflect greater attentional capture to cue information. If so, we would expect greater insula activity to predict larger validity scores, as responding to validly cued targets would be enhanced, but responding to invalidly cued targets would be hindered. However, we found the opposite, wherein greater insula activity predicted smaller validity scores. Thus, we interpret our findings to mean PTSD participants may have allocated their attentional resources to other external or internal stimuli, rendering it more difficult to pay attention to the task at hand. This is consistent with (Aupperle et al., 2016) who reported that women with PTSD had greater right insula activity during response inhibition compared to non-trauma controls, suggesting that PTSD may be associated with a deficit in the regulation of the SN.

Abnormal default mode network functional during target processing in PTSD.

We also hypothesized default mode intrusions upon task performance could account for attention abnormalities in PTSD. Our results supported this hypothesis. Increased PTSD severity was associated with greater activation of the mPFC and PCC during the validity contrast (invalidly cued targets – validly cued targets). Additionally, decreased utilization of spatial information behaviorally (smaller validity scores) was associated with greater connectivity between the right IFG (a region involved in reorienting and disengagement (Thiel et al., 2004; Weissman et al., 2006)) with DMN regions including the precuneus, PCC, angular gyrus and mPFC. Collectively, these regions are not expected to be activated during active task performance (Power et al., 2011). Our results are consistent with reports of altered DMN connectivity during rest (Bluhm et al., 2009; Clausen et al., 2017; Lanius et al., 2010; Sripada, King, Welsh, et al., 2012), suggesting that alterations observed during resting-state may

potentially reflect also alterations during active task performance. While neuroimaging studies of cognitive tasks in PTSD have implicated DMN abnormalities as well, the directionality of the findings has been mixed. Bryant et al. (Bryant et al., 2005) reported that PTSD participants showed greater mPFC activity during an auditory oddball task compared to non-trauma controls, but this group (Falconer, Allen, Felmingham, Williams, & Bryant, 2013) later reported that PTSD participants had decreased mPFC activity on a response inhibition task compared to trauma and non-trauma controls. Consistent with our findings, however, two more recent studies in PTSD reported greater mPFC activity on easier trials of the multisource interference task (Clausen et al., 2017) and Stop Signal Task (Aupperle et al., 2016) compared to controls.

One explanation for our findings is that PTSD participants were daydreaming or falling asleep during the task, as the DMN has been implicated in these processes (Buckner, Andrews-Hanna, & Schacter, 2008; Koike, Kan, Misaki, & Miyauchi, 2011). This is supported by the fact that decreased utilization of spatial information was associated with more omission errors. We do not believe this could completely account for our findings, as runs during which participants had low accuracy or were visibly falling asleep (per the MRI technician) were excluded. However, it is possible that the smaller validity scores we observed in the PTSD could reflect momentary lapses of attention during the task, during which they were mind-wandering. This could be related to a failure to suppress the DMN during target responses, such that DMN interferes with goal-directed processes (Anticevic et al., 2012). Indeed, attentional lapses have been associated with greater DMN activity (Weissman et al., 2006). There is some evidence that during the cue processing period, greater PTSD severity was associated with greater DAN – DMN connectivity. As fMRI is correlational in nature, it is difficult to determine whether SN

and DMN hyperactivity were the cause or the outcome of RT differences. However, because our task had two time windows (cues and targets), our results suggest that SN intrusions may precede DMN alterations in PTSD participants in this task.

PTSD participants show increased demands on task positive regions.

Contrary to our hypothesis, we found that participants with PTSD had enhanced recruitment of attentional control regions. PTSD severity was associated with greater activity in the putamen during the validity contrast (invalidly cued targets – validly cued targets). Additionally, increased attentional capture by spatial cues (larger validity scores) within the PTSD group was associated with greater activity in the paracentral lobule, right middle frontal gyrus, inferior operculum, ACC, fusiform, cerebellum and parahippocampus in the *Validity* contrast. Greater attentional capture within the PTSD group was also associated with greater connectivity of the right IFG to the bilateral superior and middle temporal gyri, bilateral MFG, right parahippocampus, ACC and left middle occipital gyrus in the same contrast. Although there were no differences in conflict scores behaviorally, during the *Conflict* contrast, the PTSD group had greater activation of the right insula. These findings contrast previous reports of reduced activity in attentional control regions in PTSD during oddball (Bryant et al., 2005; Felmingham et al., 2009), Go-No/Go (Falconer et al., 2008; Stevens et al., 2016) and Stroop tasks (Bremner et al., 2004; Yennu et al., 2016). Yet, our findings are in line with other studies that have reported increased recruitment of attentional control regions during stop signal (Aupperle et al., 2016) oddball (Bryant et al., 2005; Felmingham et al., 2009) and Stroop tasks (Shin et al., 2007; Thomaes et al., 2012), as well as reports of increased visual, sensory and motor processing activity during these tasks (Bryant et al., 2005; Falconer et al., 2008). We

believe that our findings may reflect an increased need to engage in task-positive regions for successful task performance (Shin et al., 2011). This may be a compensatory response to overcome DMN or SN interference. Consistent with this idea, Weissman et al. (2006) reported that attentional lapses (trials with longer RTs) were associated with greater frontal, parietal and temporal activation, possibly in order to overcome reduced sensory processing of the stimulus which resulted from the attentional lapse.

Trauma exposed controls also show differential attention processing.

Unexpectedly, the trauma exposed control group also showed altered attention processing. Behaviorally, the magnitude of their validity scores was in between that of the PTSD and NTC groups, with validity scores marginally different from the NTC group, but not different from the PTSD group. On the neural level, several patterns were similar to those observed in the PTSD group. During the processing of invalidly cued – validly cued targets (*Validity* contrast), similar to what was seen in PTSD group, decreased utilization of spatial information behaviorally (smaller validity scores) was associated with greater connectivity between the right IFG and regions of the DMN (bilateral angular gyrus, mPFC and PCC). Increased utilization of spatial information (larger validity scores) was associated with greater connectivity between the right IFG and a) attentional control regions including the SMA, bilateral MFG, IPL, SPL and, STG and b) motor and sensory processing regions including the bilateral postcentral gyri and putamen. In the same vein, during the *Conflict* contrast (incongruent – congruent targets), the TEC group also showed greater right insula activation.

The TEC group also showed patterns of brain activation and connectivity that were not present in the PTSD group. First, during the processing of spatial cues, increased utilization of

spatial information (larger validity scores) was associated with greater DAN connectivity (right MFG and right SPL seeds) across multiple neural networks (SN, DMN, VAN and DAN). Decreased utilization of spatial information was only associated with greater connectivity between the right MFG and a) the right amygdala and b) the right insula, but extending into other task positive regions such as the STG, inferior and superior parietal lobule, IFG and putamen. During conflict, the TEC group also had greater left insula and dACC activity compared to both groups.

We did not observe previously reported cognitive impairments in PTSD participants as compared to trauma-exposed controls (Hahn et al., 2015; Jenkins et al., 2010; Lagarde et al., 2010; Leskin & White, 2007; Pineles et al., 2007; Sumner et al., 2017; Sutker et al., 1995). Four of these studies (Jenkins et al., 2010; Lagarde et al., 2010; Leskin & White, 2007) did not report differences between trauma-exposed and non-trauma exposed controls. Interestingly, Levy-Gigi, Richter-Levin, Okon-Singer, Kéri, and Bonanno (2016) reported that trauma exposed individuals without PTSD showed a failure to use contextual cues in a visual discrimination task compared to healthy adults without trauma exposure. Consistent with our results, several studies have also noted that trauma exposure alone might be associated with cognitive impairment (Stein et al., 2002; Steudte-Schmiedgen et al., 2014; Danese et al., 2017; Philip et al., 2013, 2016), but not to the same degree as in participants with PTSD (Sumner et al., 2017). Collectively, this suggests that PTSD pathophysiology and trauma exposure may contribute to cognitive deficits.

Mixed results in neuroimaging findings on attentional control in PTSD may be partially related to the fact that some studies include only a non-trauma-exposed control group (Aupperle et al., 2016; Bryant et al., 2005; Felmingham et al., 2009; Thomaes et al., 2012), while others

include only a trauma-exposed control group (Clausen et al., 2017; Shin et al., 2007, 2011; Stevens et al., 2016). Thus it is unclear how these two healthy populations differ from one another. Two studies from the same research group (Falconer et al., 2008, 2013) reported that PTSD participants had altered neural activity on a response inhibition task, but that there were no differences between trauma and non-trauma controls. However a different research group (Philip et al., 2013, 2016) reported that healthy adults with a history of early life stress showed greater insula and motor activity on a working memory task, but decreased DMN activity compared to healthy adults without a trauma history, possibly indicative of compensation. None of these studies though, specifically investigated how spatial attention is affected in trauma exposure. We interpret our results to suggest that trauma exposure alone may contribute to deficits in spatial attention, but that these results are further exacerbated with increasing levels of PTSD symptoms. Furthermore, those who have been exposed to trauma may compensate for these deficits by greater recruitment of attentional control regions.

Failure to replicate resting-state functional connectivity abnormalities in PTSD.

Consistent with the literature, we found PTSD severity was associated with cross-network connectivity of ICNs at rest. Specifically, PTSD severity was associated with VAN-sensory motor (IFG – postcentral gyrus) connectivity, the latter of which was predictive of insula activity during the task. Although we found PTSD abnormalities in the SN and DMN during attention task performance, we did not observe the expected group differences in these networks at rest. Previous studies, in addition to Experiment 1, have reported greater decreased segregation of the SN and DMN (Bluhm et al., 2009; Gong et al., 2014; Kennis et al., 2015, 2016; Lanius et al., 2010; D. R. Miller et al., 2017; Nicholson et al., 2016; Raji et al., 2015; Sripada, King,

Garfinkel, et al., 2012; Yin et al., 2012), but also decreased cross network connectivity (Liu, Li, Li, Zhang, & Lu, 2017). We did, however, find that PTSD was associated with some rsFC alterations, which were predictive of task performance and brain activity. Within VAN connectivity was not predictive of behavioral performance in the PTSD group as it was in the NTC group. Additionally, greater right lateralized connectivity of the MFG and MTG was associated with faster RT to validly cued targets in PTSD, possibly consistent with the idea that greater recruitment of these regions is necessary to execute goal-directed behavior.

There are several possible reasons why we may not have replicated previous findings of greater SN and DMN cross-network connectivity at rest. First, as discussed earlier, the demographics of our sample differed from that of Experiment 1. However, studies have implicated rsFC abnormalities in both veteran (Bluhm et al., 2009; Clausen et al., 2017; Kennis et al., 2015, 2016; Miller et al., 2017; Raji et al., 2015; Sripada, King, Garfinkel, et al., 2012) and civilian populations (Lanius & Bluhm, 2010; Nicholson et al., 2016; Wu et al., 2011; Zhang et al., 2015; Zhou et al., 2012). Another possibility is that the mental states of our participants differed from those in previous studies during the resting-state scan. Several studies have shown that different mental states (e.g. passively resting vs. recalling events from the day) can affect resting-state functional connectivity patterns (Doucet et al., 2012; Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2012), something that we were unable to control for in our study. A third possibility is that because we used a seed based approach, we were unable to detect differences in other nodes of the ICNs. If we had used a connectomics approach, we might have been able to observe differences in these networks as a whole. Finally, we may not have been adequately powered to detect group differences among the three groups. The majority of rsFC in PTSD

have compared only two groups – either PTSD with trauma-exposed controls (Bluhm et al., 2009; Cao et al., 2008; Gong et al., 2014; Kennis et al., 2015, 2016; Lanius & Bluhm, 2010; Miller et al., 2007; Raji et al., 2015; Wu et al., 2011; Yin et al., 2012) or PTSD with non-trauma exposed controls (Ke et al., 2016; Nicholson et al., 2016; Zhang et al., 2016). Only two papers have included all three groups of participants, one from our laboratory reporting that the PTSD group was significantly different than both control groups (Sripada, King, Welsh, et al., 2012) and the other reporting that both PTSD and trauma exposed controls displayed abnormal rsFC compared to non-trauma exposed controls (DiGangi et al., 2016). Future studies could employ larger samples sizes to disentangle the role of PTSD symptomology and trauma exposure in resting-state functional connectivity.

Limitations

Our study had several limitations. First, we did not control for comorbid psychiatric disorders or psychiatric medication use. PTSD is highly comorbid with other mental health conditions such as depression (Lockwood & Forbes, 2014), this could have contributed to some of the variance in our findings. However, because the PTSD and TEC groups did not significantly differ, this alone is not likely to account for our findings as the TEC group did not endorse current mental health conditions or the utilization of psychiatric medications. Second, our sample size was modest and consisted of mostly females and thus, our findings may not generalize to other populations. Third, as discussed above, we were unable to control for the mental states of our participants during the resting-state scan. Fourth, as discussed in Experiment 2, the version of the ANT that we employed did not activate attentional control regions as robustly as expected. Future studies could optimize the task to better measure cue and

target related contrasts. Fifth, as discussed in Experiment 2, we employed a seed-based approach to examine rsFC. Future studies could employ connectomics to examine PTSD alterations in resting-state the ICNs in a data-driven fashion that does not rely on *a-priori* hypothesized nodes. Finally, as this study was cross-sectional, we were unable to determine causality. The fact that trauma-exposed controls manifested some attention abnormalities and that the findings were related to PTSD severity suggests that attention deficits may be the result of the trauma. However, future longitudinal studies are needed to test if they also predispose an individual to either experience trauma or develop PTSD.

Conclusion

In this study, we found that PTSD participants and to a lesser extent trauma-exposed controls, showed deficits in the utilization of spatial cues. Similar to our earlier finding during resting state, during task performance, the salience network may interfere with goal-directed attention, resulting in a reduced ability to encode contextual information. This may, in turn, influence one's propensity for attentional lapses, thus requiring greater engagement of attentional control regions to execute correct responses. Treatments which target these neural networks or cognitive deficits could be a new avenue for PTSD research.

Chapter IV Tables

Table 4.1.

Positive correlation of PTSD symptom severity (CAPS) with brain activity in PTSD group

Contrast	Regressor	Brain Region	Cluster size	MNI Coordinates (x y z)	Analysis (z)	*p* (FWE)
Orienting	CAPS total	L putamen, L insula, R caudate	207	-26 -4 16	4.19	0.001
		L amygdala	8	-27 -4 -14	3.44	0.217 (SVC)
	Intrusion	L thalamus	102	-24 -19 16	3.91	0.043
		L putamen	18	-24 2 16	3.41	0.029 (SVC)
	Avoidance	No sig clusters				
	Alterative in mood and cognitions	L insula, MFG, IFG, precentral gyrus	210	-24 2 19	4.11	0.001
	Hyperarousal	Cerebellum	344	21 -67 -26	4.84	<0.001
Validity	CAPS total	R putamen	200	27 -10 4	4.30	0.007
		L putamen	83	-18 11 4	3.42	0.241
		mPFC, dACC	195	-3 47 4	3.70	0.009
		PCC	131	-3 -61 10	3.41	0.054
	Intrusion	R putamen	6	30 -13 7	2.90	0.082 (SVC)
	Avoidance	R putamen	2	30 -7 7	3.39	0.121 (SVC)
		PCC	23	-3 -43 28	3.10	0.975
	Alterations in mood and cognitions	R putamen	9	30 -10 7	2.88	0.064 (SVC)
		PCC	8	-9 -58 13	3.07	0.070 (SVC)
	Hyperarousal	L caudate	250	-21 26 13	4.89	0.002

Note. CAPS, clinical administered PTSD scale; dACC, dorsal anterior cingulate cortex; FWE, family-wise error; IFG, inferior frontal gyrus; L, left; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; R, right, SVC, small volume corrected

Table 4.2.
Correlation of validity scores with brain activity during Validity

Contrast Map	Brain Region	Cluster Size	MNI Coordinates (x y z)	Analysis (z)	*p* (FWE)
Group x RT (PTSD, NTC)	Paracentral lobule, mPFC, parietal lobe, L precuneus, bilateral postcentral gyrus, R SMA	232	-15 -37 58	5.17	0.001
	MFG, ACC, R frontal inferior operculum, mPFC, precentral gyrus, R SPL	360	30 8 31	4.55	<0.001
	R fusiform, parahipp, R lingual gyrus, cerebellum	164	30 -49 -5	3.66	0.011
NTC negative	Paracentral lobule	136	-18 -40 58	4.35	0.007
	R precentral gyrus	115	30 -10 25	3.73	0.018
	rACC	110	6 29 1	3.63	0.022
	R fusiform, parahipp	17	30 -49 -5	3.46	0.984
PTSD positive	IFG, MFG, ACC	539	30 8 31	4.64	<0.001
	Precuenus, PCC, SPL, sup occ gyrus	549	21 -79 46	4.16	<0.001
	Fusiform MTG, mid occ	7 67	24 -64 -5 54 -49 -11	3.15 3.46	1.000 0.295

Note. FWE, family-wise error; IFG, inferior frontal gyrus; L, left; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; mPFC, medial prefrontal cortex; MTG, middle temporal gyrus; parahipp, parahippocampus; PCC, posterior cingulate cortex; occ, occipital; R, right, rACC, rostral anterior cingulate cortex; SMA, supplementary motor area; SPL, superior parietal lobule; sup, superior

Table 4.3.
Correlation of PTSD symptom severity (CAPS) with on-task connectivity in PTSD group

Contrast	Regressor	Brain Region	Cluster size	MNI Coordinates (x y z)	Analysis (z)	*p* (FWE)
Orienting MFG seed	CAPS total pos	L cerebellum	102	-27 -79 -35	4.47	0.053
		R cerebellum	203	12 -79 -29	3.97	0.001
		R angular gyrus	156	42 -55 40	3.96	0.007
		Superior medial frontal gyrus	103	6 44 37	3.72	0.051
	CAPS total neg	No sig clusters				
	Intrusion	No sig clusters				
	Avoidance	Superior medial frontal gyrus	11	6 38 43	3.37	0.053 (SVC)
		R cerebellum	213	18 -43 -17	4.59	0.001
	Alterations in mood & cognitions	R cerebellum	7	12 -76 -35	3.09	0.077 (SVC)
	Hyperarousal	No sig clusters				
Orienting SPL seed	CAPS total pos	No sig clusters				
	CAPS total neg	Precuneus	131	-3 -67 52	3.89	0.021
	Intrusion		7	-3 -70 43	3.41	0.077 (SVC)
	Alterations in mood & cognitions		3	6 -67 55	2.96	0.121 (SVC)
	Hyperarousal					
Validity MFG and IFG seeds	No sig clusters					

Note. CAPS, clinical administered PTSD scale; FWE, family-wise error; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; neg, negative; pos, positive; R, right, sig; significant; SPL, superior parietal lobule; SVC, small volume corrected

Table 4.4.
Correlation of validity scores with on-task connectivity during Orienting (MFG seed)

Contrast Map	Brain Region	Cluster Size	MNI Coordinates (x y z)	Analysis (z)	*p* (FWE)
Group x RT (TEC, NTC)	R IPL, IFG, MFG, precuneus, precentral gyrus, supramarginal gyrus, R precentral, R postcentral, SPL, angular, MTG, caudate, sup occ	1721	39 -1 25	4.18	<0.001
	R STG, putamen	274	24 -13 1	3.85	<0.001
	Midbrain, thalamus	159	0 – 7 -8	3.74	0.008
	Midbrain, cerebellum, parahipp	224	6 -22 -17	4.35	0.001
	R STG, insula	130	39 -37 13	4.06	0.022
	L precentral	242	-30 -22 58	3.92	0.001
	mPFC, medial orbital frontal cortex	213	-18 53 -5	3.80	0.001
	mPFC, SFG	135	15 32 55	3.79	0.018
TEC pos	R midbrain, vermis, parahipp bilateral cerebellum	329	6 -25 -14	4.72	<0.001
	L MFG, mPFC, L orbital frontal cortex	427	-21 35 -5	4.35	<0.001
	R STG, insula, thalamus, hipp	216	36 -46 16	4.31	0.001
	R mid cingulate, SMA	116	18 -7 40	4.01	0.037
	L precentral, postcentral, IPL	601	-33 -22 58	4.30	<0.001
	L fusiform, parahipp, hipp, MTG	329	-36 -49 -17	3.99	<0.001
	R MFG	108	33 23 19	3.73	0.050
TEC neg	R amygdala, STG, midbrain, putamen, hipp, parahipp, thalamus	715	30 -1 -11	4.52	<0.001
	R IPL, IFG, MFG, insula, precentral, supramarginal, bilateral precuneus, angular, SPL, mid-cingulate	2394	48 -37 37	4.35	<0.001
	R SFG, MFG	130	24 8 55	4.34	0.022
NTC pos	No sig clusters				
NTC neg	L orbital frontal cortex	30	-21 56 -2	4.23	0.015 (SVC)

Table 4.5.
Correlation of validity scores with on-task connectivity during Orienting (SPL seed)

Contrast Map	Brain Region	Cluster Size	MNI Coordinates (x y z)	Analysis (z)	*p* (FWE)
Group x RT (TEC, NTC)	Bilateral mPFC, IFG, SFG, dACC, MFG, orbital frontal, L insula, L putamen, L amygdala, L parahipp, L caudate, L hipp	3137	51 20 16	4.71	<0.001
	Bilateral STG, MTG, thalamus, precuneus, PCC, R hipp, parahipp, thalamus, mid occ, L angular gyrus, L hipp, R caudate, insula, R amygdala	3285	0 -16 13	4.68	<0.001
	L precuneus, post central gyrus, paracentral lobule	129	-6 -43 70	4.06	0.028
TEC pos	Bilateral IFG, mPFC, SFG, STG, MTG, ACC, MFG, thalamus, precuneus, medial SFG, precuneus, parahipp, insula, PCC, mid occ, oribital frontal cortex, hipp, supramarginal gyrus, hipp, angular gyri, caudate, midbrain, paracentral lobule, putamen, SMA, IPL, cuneus, amygdala	9712	-3 26 4	5.15	<0.001
TEC neg	R precentral	119	54 -1 37	3.61	0.040
NTC pos	No sig clusters				
NTC neg	No sig clusters				

Note. dACC, dorsal anterior cingulate cortex; FWE, family-wise error; hipp, hippocampus; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L, left; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; mPFC, medial prefrontal cortex; MTG, middle temporal gyrus; occ, occipital; parahipp, parahippocampus; PCC, posterior cingulate cortex; R, right, sig; significant; SFG, superior frontal gyrus; SMA, supplementary motor area; SPL, superior parietal lobule; sup, superior; STG, superior temporal gyrus; SVC, small volume corrected

Table 4.6.

Correlation of validity scores with on-task connectivity during Validity (IFG seed)

Contrast	Brain Region	Cluster size	MNI Coordinates (x y z)	Analysis (z)	*p* (FWE)
Group x RT (PTSD, NTC)	Medial frontal gyrus, ACC, R MFG	342	36 26 22	3.86	<0.001
	L MTG, mid occ gyrus, parahipp, STG, hipp	260	-39 -46 1	3.65	<0.001
	R STG, MTG, parahipp, cerebellum, fusiform, hipp	480	45 -16 -8	3.56	<0.001
	Paracentral lobule, medial frontal gyrus, R postcentral gyrus, SMA, L precuneus	184	6 -28 64	3.48	0.004
	R IFG, MFG, SFG	152	54 35 4	3.65	0.011
	R MFG, precentral gyrus, IFG, frontal operculum	244	48 -1 46	3.48	0.001
	L SPL, mid occ, precuneus	126	-21 -70 49	3.47	0.027
Group x RT (NTC, TEC)	R postcentral gyrus, IPL, supramarginal gyrus, insula, STG, putamen	890	33 -16 4	4.03	<0.001
	L insula, STG, operculum, putamen	118	-42 -1 1	3.87	0.036
	L IPL, postcentral gyrus, precentral gyrus, supramarginal gyrus, SFG, SMA	753	-36 -37 55	3.69	<0.001
	R MFG, IFG, SFG	143	27 32 28	3.47	0.015
	L angular gyrus, MTG, STG, IPL, supramarginal gyrus, precuneus	481	-36 -70 34	4.70	<0.001
	Precuneus, PCC, calcarine, cuneus	671	6 -55 25	4.36	<0.001
	Medial and sup frontal gyrus, rACC, frontal medial orbital cortex, R IFG, R insula	1624	6 56 34	4.18	<0.001
	L precentral gyrus	112	-27 8 31	4.06	0.045
PTSD positive	L STG, MTG	207	-39 17 -25	3.79	0.002
	R MFG, IFG	106	36 26 22	3.78	0.056
	L MTG, mid occ gyrus, STG	173	-48 -43 1	3.71	0.005
	R STG, MTG, parahipp	456	48 -13 -8	3.69	<0.001
	L MFG, sup medial frontal gyrus, ACC	119	-15 41 16	3.59	0.035
PTSD negative	Precuneus, PCC, inf/sup parietal lobe, angular gyrus, cuneus	1503	-21 -58 52	3.77	<0.001
	R IFG, MFG, medial frontal gyrus	208	51 38 1		0.002

	L putamen, thalamus, insula	225	-24 5 1		0.001
	SMA, mid-cingulate, sup frontal gyrus, medial prefrontal gyrus	231	3 2 55		<0.001
	mid and sup frontal gyrus, IFG, medial frontal gyrus	483	18 44 34		<0.001
TEC positive	L insula, IPL, postecentral gyrus, STG, precentral gyrus, sup parietal, SMA, MFG	1373	-42 -1 1	4.25	<0.001
	R putamen, insula, STG, operculum, IFG	405	30 -16 4	4.13	<0.001
	R postcentral gyrus, IPL, supramarginal gyrus, precuneus, SPL	952	39 -31 46	3.90	<0.001
	R MFG, IFG, SFG	187	27 32 28	3.72	0.003
	L insula, putamen	131	-36 -16 1	3.48	0.023
TEC negative	Precuneus, PCC, calcarine, cuneus	544	0 -70 31	4.53	<0.001
	R angular gyrus, STG, supramarginal gyrus	463	54 -55 37	4.37	<0.001
	L angular gyrus, STG, IPL	433	-36 -70 34	4.29	<0.001
	Medial frontal gyrus	437	30 50 -8	4.24	<0.001
	Medial and sup frontal gyrus, ACC	974	24 -13 37	3.98	<0.001
	L MFG, inferior orbital gyrus	172	-36 44 7	3.84	0.006
NTC positive	No sig clusters				
NTC negative	No sig clusters				

Note. ACC, anterior cingulate cortex; FWE, family-wise error; hipp, hippocampus; inf, inferior; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L, left; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; MTG, middle temporal gyrus; occ, occipital; parahipp, parahippocampus; PCC, posterior cingulate cortex; R, right, rACC, rostral anterior cingulate cortex; SFG, superior frontal gyrus; sig; significant; SMA, supplementary motor area; SPL, superior parietal lobule; sup, superior; STG, superior temporal gyrus

Table 4.7.

Correlation of validity scores with resting state functional connectivity

Seed	Contrast	Brain Region	Cluster size	MNI Coordinates (x y z)	Analysis (z)	*P* (FWE)
IFG	Group x RT (NTC,PTSD)	L IFG, frontal inf operculum, precentral gyrus, STG, MFG, insula	272	-42 26 10	4.99	<0.001
	PTSD neg	R precentral, postcentral, supramarginal, IFG, IPL	253	66 -13 25	4.12	<0.001
		L STG, rolandic operculum	106	-54 14 -5	3.70	0.062
		L IFG	31	-42 26 10	4.11	0.948
	NTC pos	L IFG, frontal inf operculum, precentral gyrus	128	-48 1 13	4.37	0.029
MFG	Group x RT (PTSD,NTC)	R MTG, mid occ,	120	39 -61 4	3.89	0.043
		R MTG, STG, inf temp	192	72 -16 -20	4.29	0.003
	PTSD pos	Midbrain, thalamus, parahipp	119	9 -25 -2	3.81	0.045
		R MTG	35	42 -52 1	2.99	0.906
	PTSD neg	R MTG, Inf temp, temp pole	235	51 -19 -14 72 -16 -20	4.30 3.79	0.001
	NTC neg	R MTG	13	39 -61 10	3.07	1.00
dACC		No sig clusters				
PCC	Group x RT (PTSD,NTC)	L MFG	112	-39 50 31	3.89	0.05
	PTSD pos	L MFG	55	-39 32 37	3.11	0.515
	NTC neg	L MFG	13	-39 50 31	3.52	1.00

Note. dACC, dorsal anterior cingulate cortex; FWE, family-wise error; inf, inferior; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; L, left; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; MTG, middle temporal gyrus; neg, negative; NTC, non-trauma-exposed control; occ, occipital; parahipp, parahippocampus; PCC, posterior cingulate cortex; pos, positive; PTSD, posttraumatic stress disorder; R, right; sig; significant; STG, superior temporal gyrus; temp, temporal

Table 4.8.
Exploratory ANOVA of group differences in brain activation on the ANT

Contrast Map and Brain Region	Cluster Size	MNI Coordinates (x y z)	Analysis (z)	*p* (SVC)
Alerting		No significant clusters		
Disengagement		No significant clusters		
Conflict – main effect of group				
R Insula	22	42 -10 10	3.76	0.032
L Insula	12	-42 -4 10	3.71	0.038
ACC	21	3 -4 34	3.28	0.142

Post-hoc tests of group differences in brain activation during conflict

Contrast Map and Brain Region	Cluster Size	MNI Coordinates (x y z)	Analysis (z)	*p* (FWE)
PTSD-NTC				
R insula	47	39 -16 10 33 -7 13	3.71 3.09	0.007 SVC
PTSD-TEC		No sig clusters		
TEC-PTSD				
L insula	30	-42 -4 10	4.05	0.015
ACC	61	3 -4 31	3.82	0.003
TEC-NTC				
R insula	173	39 -10 13	4.36	0.005 SVC
L insula	243	-30 -25 13	4.19	0.001
ACC	41	0 -4 34	3.46	0.008
NTC-PTSD		No sig clusters		
NTC-TEC		No sig clusters		

Note. ACC, anterior cingulate cortex; FWE, family-wise error; L, left; MNI, Montreal Neurological Institute; NTC, non-trauma-exposed control; PTSD, posttraumatic stress disorder; R, right; sig; significant; SVC, small volume corrected; TEC, trauma-exposed control

Chapter IV Figures

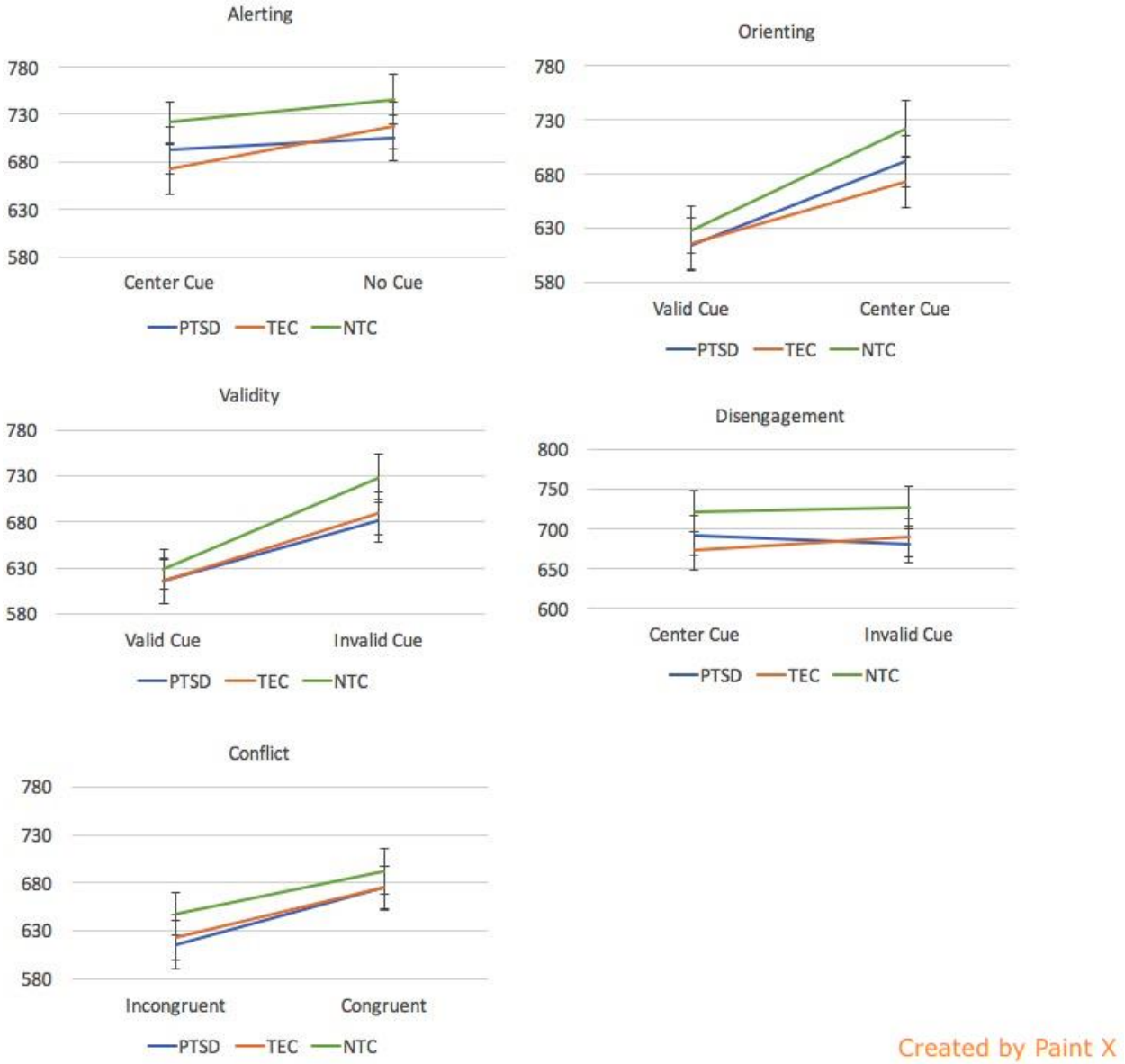

Figure 4.1. Group differences in ANT behavioral effects.
ANT, attention network task; NTC, non-trauma-control; PTSD, posttraumatic-stress disorder; TEC, trauma-exposed control. The NTC group showed a significantly larger validity effect compared to the PTSD group, and a marginally larger validity effect compared to the PTSD group. There were no differences between the PTSD and TEC groups in validity. There were no group differences in alerting, orienting, disengagment or conflict effects.

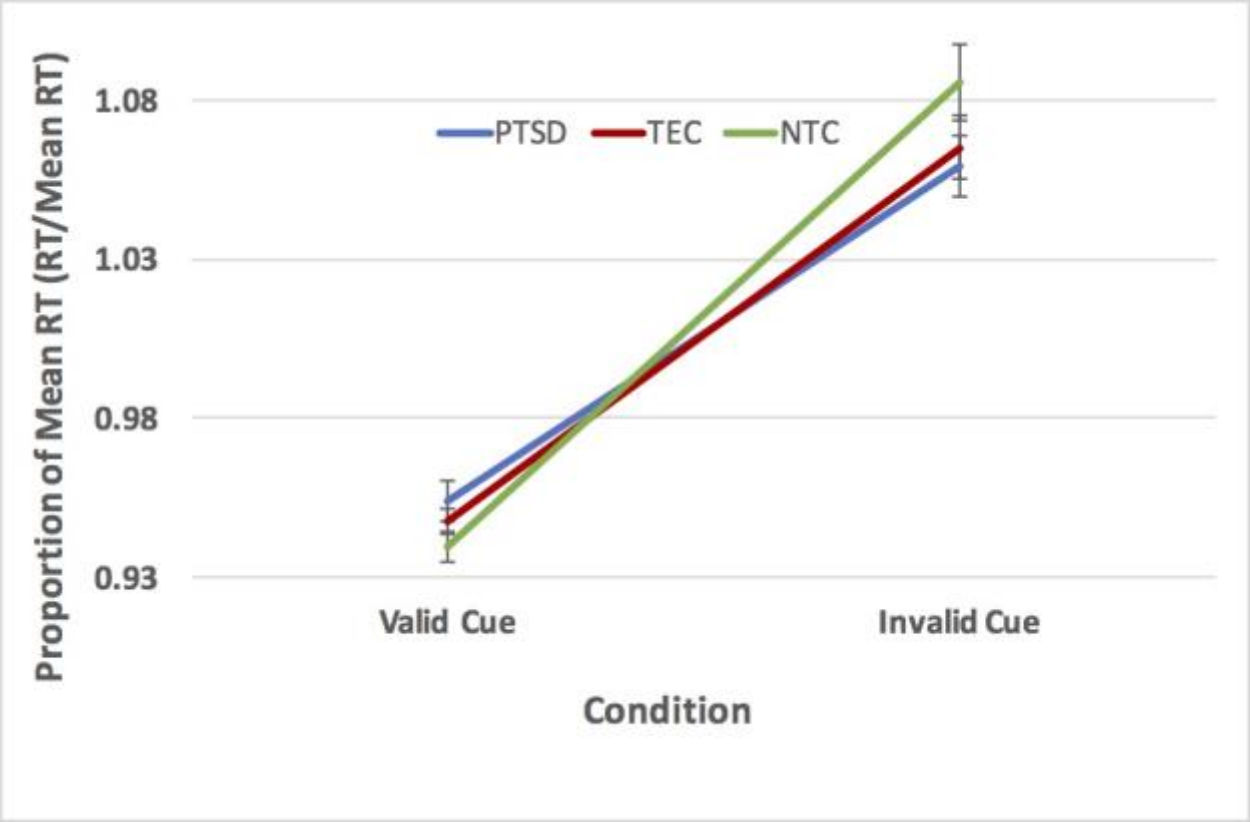

Figure 4.2. Group differences in the behavioral validity effect as a proportion of mean reaction time.

NTC, non-trauma-control; PTSD, posttraumatic-stress disorder; TEC, trauma-exposed control; RT, reaction time. When controlling for mean RT, the PTSD group had smaller validity scores compared to the NTC group, driven by slower RT in valid cue trials and faster RT in invalid trials.

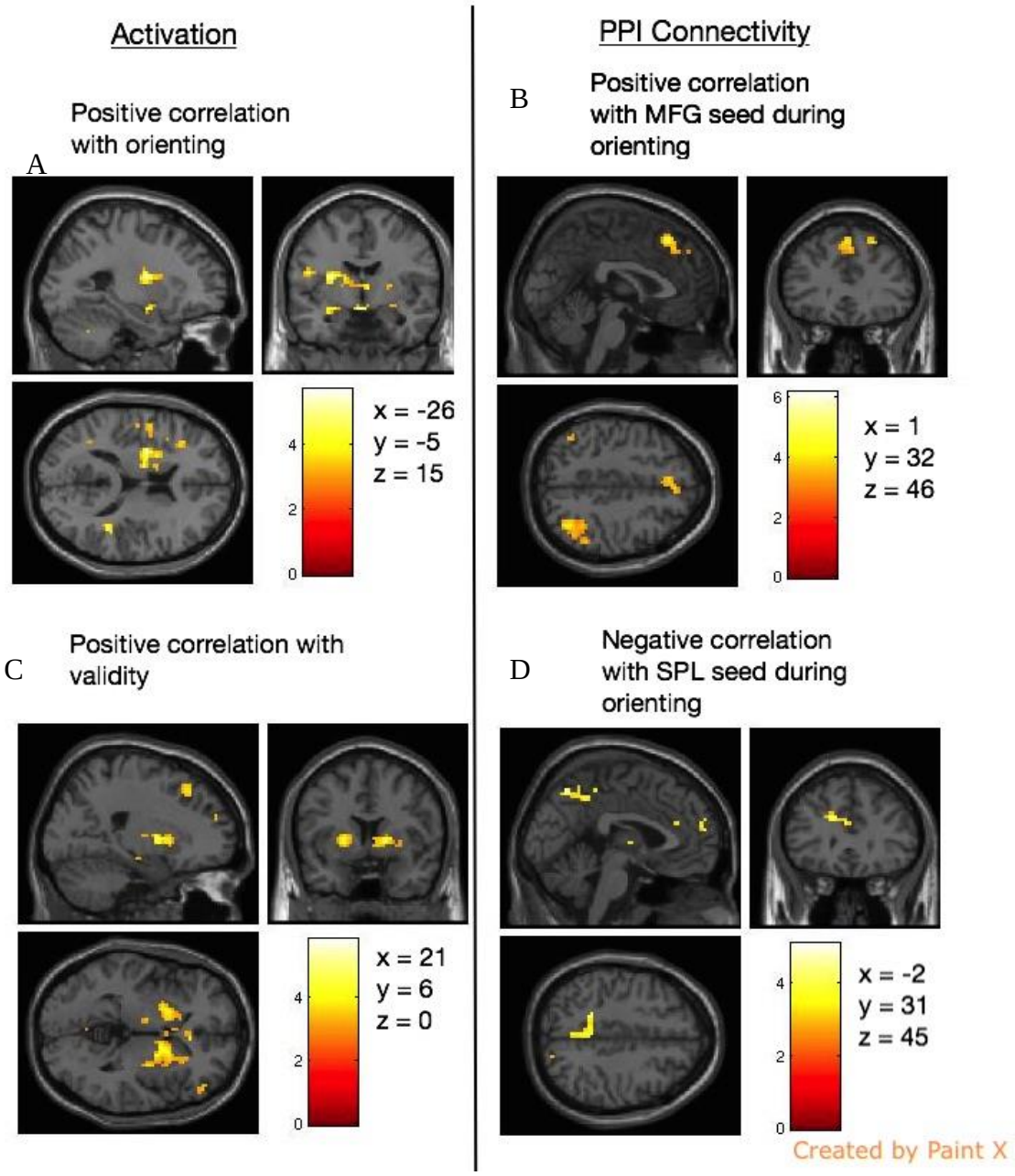

Figure 4.3. Total CAPS scores predicting brain activity and connectivity during the ANT in PTSD group. $p < 0.005$ uncorrected. ANT, attention network test; CAPS, clinician-administered PTSD scale; PTSD, posttraumatic stress disorder; SPL, superior parietal lobule; MFG, middle frontal gyrus; PPI, psychophysiological interaction. A) Total CAPS scores were positively correlated with activation in the left putamen/insula in the *Orienting* contrast, B) Total CAPS scores positively correlated with connectivity with the MFG seed and the bilateral cerebellum, the right angular gyrus and the superior medial frontal gyrus in the *Orienting* contrast. C) Total CAPS scores were positively correlated with activity in the right putamen, mPFC, dACC and the PCC in the *Validity* contrast. D) Total CAPS scores were negatively correlated with connectivity between the right SPL seed the precuneus in the *Orienting* contrast.

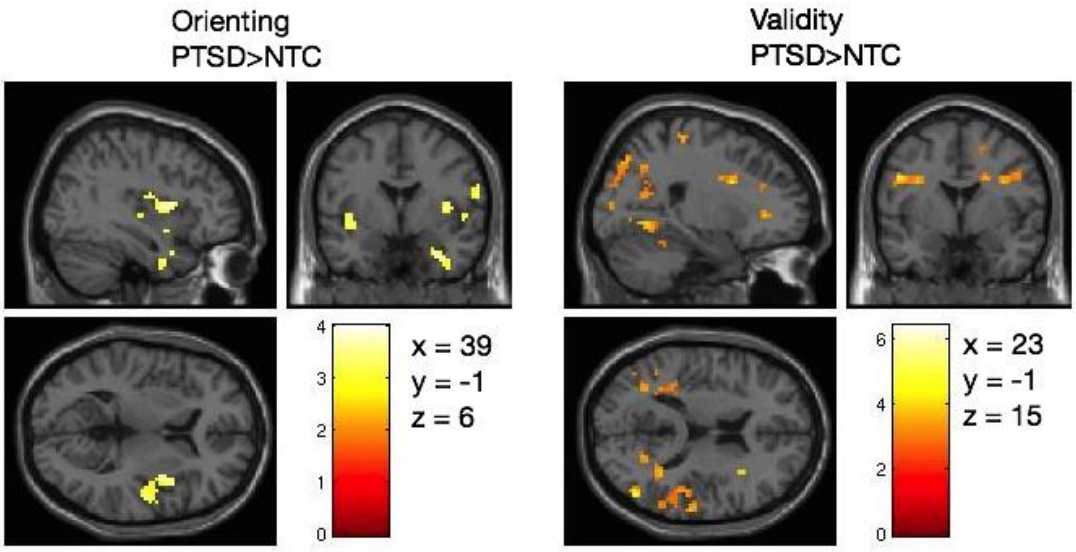

Figure 4.4. Interaction of group x behavioral validity scores x brain activity.
$p < 0.005$ uncorrected. NTC, non-trauma-control; PTSD, posttraumatic-stress disorder. Left: In the PTSD group, smaller validity scores were correlated with more right insula activity, but in the NTC group, larger scores were correlated with more right insula activity in the *Orienting* contrast. Right: In the PTSD group, validity scores were positively correlated with activity in a) the paracentral lobule extending to the precuneus, SMA, medial frontal gyrus and postcentral gyri, b) the right middle frontal gyrus extending to the anterior cingulate cortex, inferior operculum and superior frontal gyrus and c) the right fusiform extending to the parahippocampal gyrus and cerebellum in the *Validity* contrast. In the NTC group, these areas were negatively correlated with validity scores.

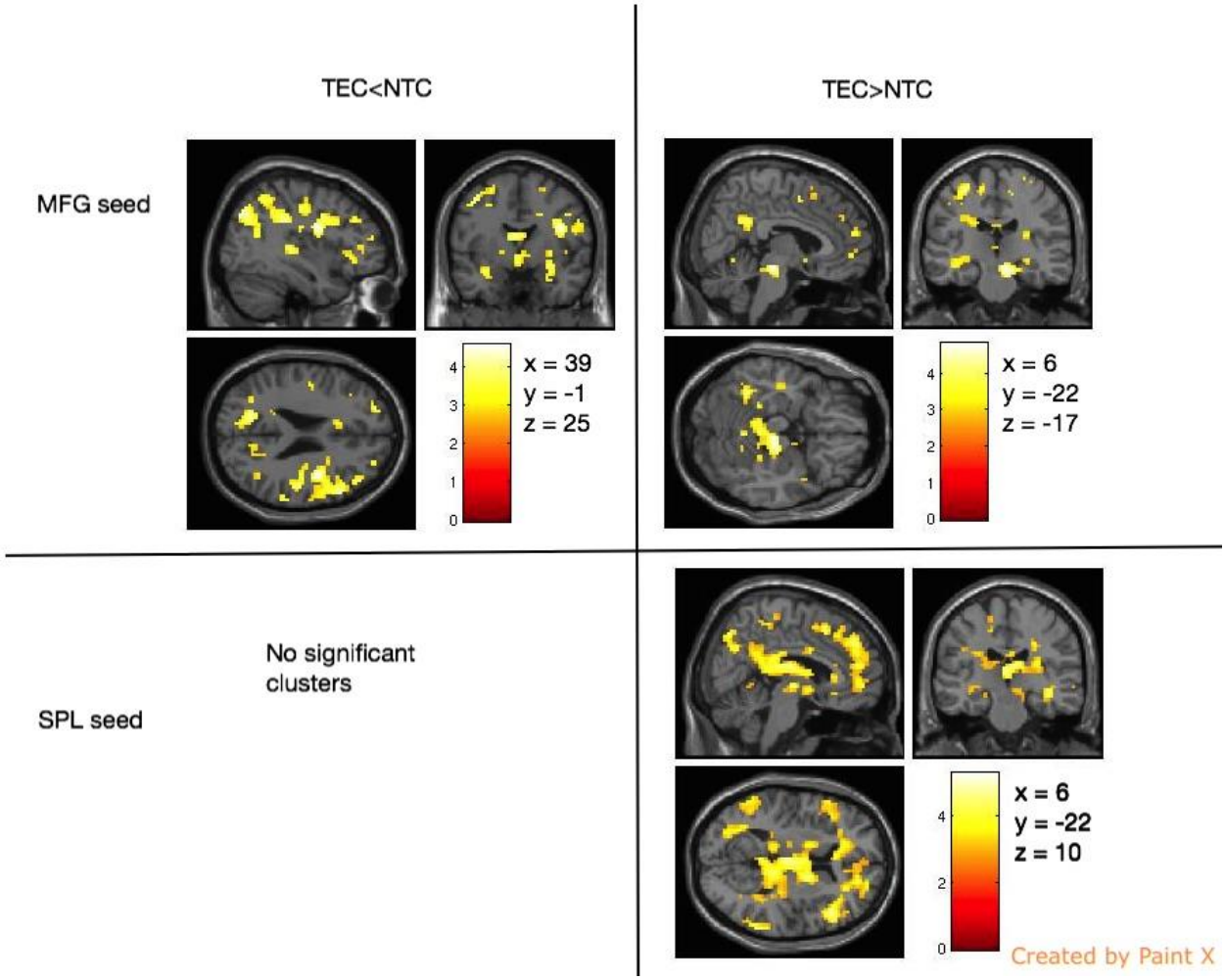

Figure 4.5. Group x behavioral validity scores x brain connectivity during *Orienting*.
$p < 0.005$ uncorrected. MFG, middle frontal gyrus; NTC, non-trauma-control; PTSD, posttraumatic-stress disorder; SPL, superior parietal lobule; TEC, trauma-exposed control.
Top row: In the TEC group, greater connectivity of the MFG with a) the right midbrain/parahippocampus/cerebellum, b) the right superior temporal gryus/insula, c) the mid-cingulate/supplementary motor area, d) the left precentral gyrus/inferior parietal lobule, e) the left fusiform/hippocampus and f) the right MFG was associated with larger validity scores. In contrast, in the TEC group, greater connectivity of the MFG with a) the right amygdala extending to the superior temporal gyrus, putamen, midbrain and hippocampus, b) the right inferior parietal lobule extending to the inferior frontal gyrus, MFG, insula, supramarginal gyrus, angular gyrus, SPL and mid-cingulate and c) the right superior frontal gyrus was associated with larger validity scores. Connectivity was not associated with validity scores in the NTC group.
Bottom row: In the TEC group, greater connectivity of the SPL with a) a large cluster encompassing the bilateral PFC, left insula, left putamen and left hippocampus, b) a more posterior cluster encompassing the bilateral temporal lobe, posterior cingulate cortex, precuneus, middle occipital gyrus, right caudate, left angular gyrus, right insula and right amygdala and c) the left precuneus/paracentral lobule was associated with larger validity scores. None of these regions were correlated with connectivity in the NTC group.

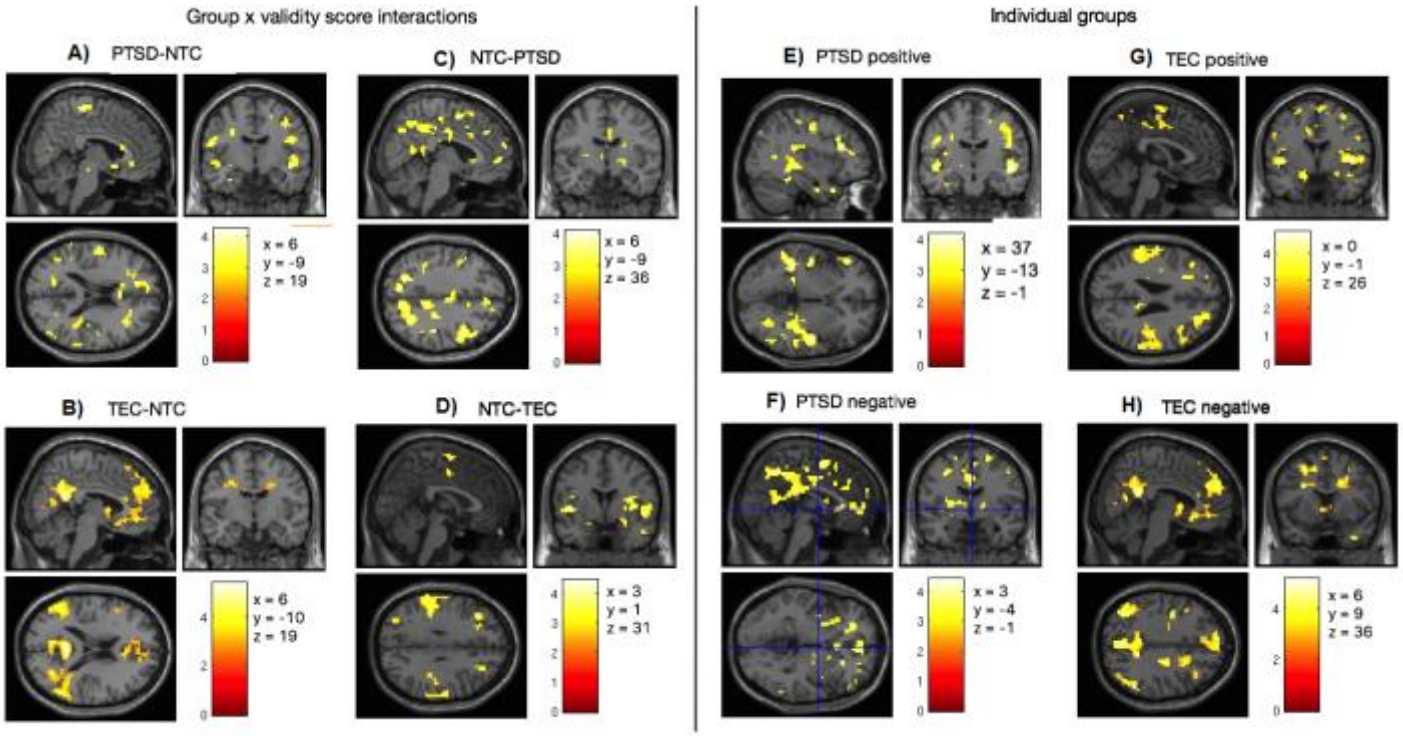

Figure 4.6. Group x behavioral validity scores x brain connectivity in the *Validity* contrast with the IFG seed.
$p < 0.005$ uncorrected. NTC, non-trauma-control; PTSD, posttraumatic-stress disorder; TEC, trauma-exposed control; IPL, inferior parietal lobule; STG, superior temporal gyrus; MFG, middle frontal gyrus; MTG, middle temporal gyrus. A) Group (PTSD-NTC) x validity score interaction of the IFG seed connectivity with bilateral STG, MTG, and MFG. B) Group (TEC-NTC) x validity score interaction of IFG seed connectivity with the left angular gyrus, precuneus, medial and superior frontal gyrus, and left precentral gyrus. C) Group (NTC-PTSD) x validity score interaction of IFG seed connectivity with the medial frontal gyrus, paracentral lobule, superior parietal lobule and IFG. D) Group (NTC-TEC) x validity score interaction of IFG seed connectivity with the right postcentral gyrus, left insula, left IPL and right MFG. E) In the PTSD group, greater connectivity of the IFG with the STG, MTG, and MFG were associated with larger validity scores. F) In the PTSD group, greater connectivity of the IFG with the precuneus/posterior cingulate, medial frontal gyrus, left putamen and supplementary motor area/ mid cingulate cortex was associated with smaller validity scores. G) In the TEC group, greater connectivity of the IFG with the bilateral insula, left superior parietal lobe, right putamen, right postcentral gyrus and right MFG was associated with larger validity scores. H) In the TEC group greater connectivity of the IFG with bilateral angular gyri, medial and superior frontal gyrus and left MFG extending to the inferior orbital gyrus was associated with smaller validity scores. IFG seed connectivity was not correlated with validity scores in the NTC group.

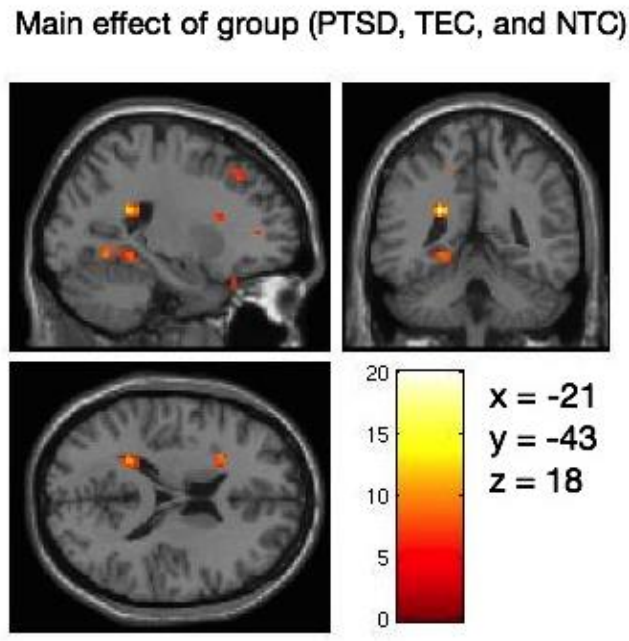

Figure 4.7. One-way ANOVA of resting-state functional connectivity with dACC seed.
$p < 0.005$ uncorrected. dACC, dorsal anterior cingulate cortex; NTC, non-trauma-control; PTSD, posttraumatic-stress disorder; TEC, trauma-exposed control.
A one-way ANOVA showed that there was a significant group difference of dACC connectivity with a parietal white matter bundle just dorsal to the left ventricle, which was outside of the search masks ([-24 -46 22], k = 30, z = 4.99, $p = 0.024$ whole brain FWE). These areas were positively connected in the NTC group ([-24 -46 22], k = 5.30, $p = 0.015$ SVC), but were not connected in the PTSD or TEC groups. There were no group differences in resting-state functional connectivity with the inferior frontal gyrus, middle frontal gyrus or posterior cingulate seeds.

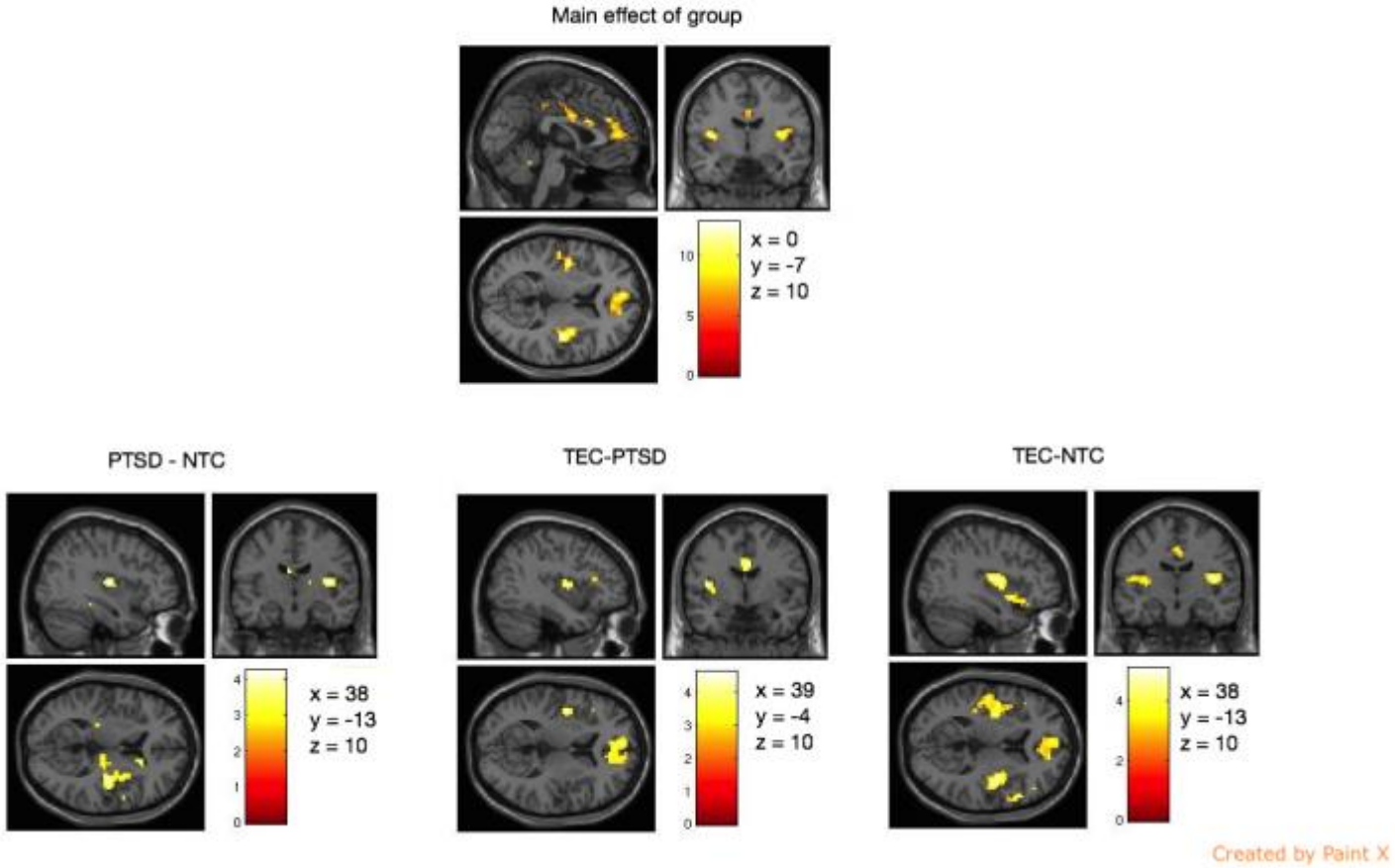

Figure 4.8. Group differences in brain activity during conflict.

$p < 0.005$ uncorrected. NTC, non-trauma-control; PTSD, posttraumatic-stress disorder; TEC, trauma-exposed control.

There was a significant main effect of group during the *Conflict* contrast in the bilateral insula and anterior cingulate. The PTSD and TEC groups had greater right insula activity compared to the NTC group, while the TEC group had greater left insula and anterior cingulate activity compared to both the PTSD and NTC groups. There were no significant results for the PTSD>TEC or NTC>TEC comparisons

CHAPTER V

General Discussion

This dissertation utilized behavioral and neuroimaging data to better understand attentional deficits in PTSD with a central hypothesis that PTSD is associated with disruptions of neural networks involved in attention, which may underlie difficulty with emotion regulation. To our knowledge, this is the first research to combine attention measures of neural connectivity, activation and behavioral performance in PTSD. Specifically, we examined 1) the type of behavioral attentional impairment present in PTSD, 2) the relationship between resting-state functional connectivity, behavioral performance and on-task activation/connectivity and 3) the neural mechanisms of attentional impairments in PTSD.

Our results are two-fold. First, we demonstrated that large scale intrinsic connectivity networks present at rest are predictive to some degree of attention-task neural activation, connectivity and behavioral performance, although these relationships are not necessarily intuitive (i.e. according to theoretical models dominant in the literature). This offers promise that resting-state measures could one day used as an alternative to active tasks, to study brain function. However, there is still a great deal to learn regarding the specific ways that resting-state is related to active tasks, as we found that the relationships between rest and task differed depending on the task condition, network node and task measure (i.e. activation vs connectivity). As Power and Peterson (2013, p. 6) who have contributed seminal work in the fields of resting-

state functional connectivity and attention noted, "A great deal of work remains to be done to characterize the specific contributions of particular regions to [cognitive] control."

Second, in two heterogeneous samples of PTSD participants, we demonstrated that spatial attention is disrupted. We found that alterations of two intrinsic connectivity networks - the salience and default mode networks – which have been shown to be abnormal in PTSD at rest also showed abnormal functioning while attending to an orienting task. Our results suggest a possible mechanism of attention disruptions in PTSD, by which the salience network interferes with goal-directed attention, resulting in a reduced ability to encode contextual information. This in turn may influence one's propensity for attentional lapses, thus requiring greater engagement of attentional control regions to execute correct responses.

Understanding attentional processes in PTSD may one day lead to novel treatments. Interventions that utilize attention training, such as mindfulness (Shapiro et al., 2006) might be useful for alleviating attentional impairments. We recently demonstrated that mindfulness training was associated with changes in resting-state functional connectivity of attentional control and default mode regions (King, Block, Sripada, Rauch, Giardino, et al., 2016). Patients might be also able learn to modify affected neural networks by practicing tasks that rely on these same circuits (Vinogradov, Fisher, & de Villers-Sidani, 2012). Medications which affect attention are another avenue for treatment. McAlister et al. (2016) demonstrated that a methylphenidate trial improved PTSD symptoms and additional stimulant trials are underway. Additionally, brain stimulation and neuromodulation offer methods of targeting affected neural networks directly. Technologies such as deep brain stimulation and transcranial magnetic stimulation have already been used with other psychiatric populations with promising success

(Ressler & Mayberg, 2007). Moreover, real-time fMRI neurofeedback has been demonstrated to be a feasible method to modulate resting-state neural networks (Gerin et al., 2016; Ruiz, Buyukturkoglu, Rana, Birbaumer, & Sitaram, 2014).

The dynamic interplay of human brain networks is complex, yet, our understanding of brain functioning as a whole has dramatically increased since the first characterization of the default mode network in 2001 (Raichle et al., 2001). Future research will continue to reveal novel insights about the inner workings of the human mind, which we hope will inform our understanding of psychiatric disorders.

APPENDIX A: ADHD History

ADHD History

Previous Diagnosis and Treatments:

Current Symptoms:

Inattention

- Inability to focus/sustain attention
- Distractibility by external stimuli
- Distractibility by extraneous thoughts
- Difficulty multitasking
- Difficulty shifting attention from one task to another
- Indecision, difficulty recalling and organizing details required for a task
- Poor time management, losing track of time
- Avoiding tasks or jobs that require sustained attention
- Procrastination
- Difficulty initiating tasks
- Difficulty completing and following through on tasks

Hyperactivity

- Restless/ Full of energy
- Fidgets/ Can't sit still
- Chooses highly active, stimulating jobs
- Avoids situations with low physical activity or sedentary work
- May choose to work long hours or two jobs
- Seeks constant activity
- Easily bored

Impulsivity

- Impatient (e.g., wants people to get to the point, often speeds while driving, cuts into traffic to go faster than others).
- Intolerant to frustration, easily irritated
- Impulsive, snap decisions and irresponsible behaviors
- Loses temper easily, angers quickly
- Often acts without thinking of consequences
- Often rushes through activities or tasks, is fast paced (e.g., averse to doing things carefully and systematically).
- Often has difficulty resisting immediate temptations or appealing opportunities, while disregarding negative consequences (commits to a relationship after brief acquaintance, takes job or enters into business arrangement without doing due diligence).

Family history of ADHD

Educational History (Note #years of education completed)

Stage	Grades/Performance	Behaviors
Preschool/ Kindergarten		
Grades 1-3		
Grades 4-6		
Diagnosis of ADHD before age 7?		
Middle school		
High School		
College		
Post-College		
Work		

Special Education

- LD class
- Behavioral/emotional class
- Resource room
- Speech and language therapy

Occupational history

- History of employment/Reasons for termination
- Current employment, perceptions of co-workers, managers, worries about termination

Interpersonal history

- Childhood relationships with/perceptions of siblings and friends.
- Current relationships with/perceptions of significant other/immediate family
- Current relationships with/perceptions of friends

APPENDIX B: Beck Depression Inventory II

BDI-II

Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness
- 0 I do not feel sad.
- 1 I feel sad much of the time.
- 2 I am sad all the time.
- 3 I am so sad or unhappy that I can't stand it.

2. Pessimism
- 0 I am not discouraged about my future.
- 1 I feel more discouraged about my future than I used to be.
- 2 I do not expect things to work out for me.
- 3 I feel my future is hopeless and will only get worse.

3. Past Failure
- 0 I do not feel like a failure.
- 1 I have failed more than I should have.
- 2 As I look back, I see a lot of failures.
- 3 I feel I am a total failure as a person.

4. Loss of Pleasure
- 0 I get as much pleasure as I ever did from the things I enjoy.
- 1 I don't enjoy things as much as I used to.
- 2 I get very little pleasure from the things I used to enjoy.
- 3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings
- 0 I don't feel particularly guilty.
- 1 I feel guilty over many things I have done or should have done.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

6. Punishment Feelings
- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

7. Self-Dislike
- 0 I feel the same about myself as ever.
- 1 I have lost confidence in myself.
- 2 I am disappointed in myself.
- 3 I dislike myself.

8. Self-Criticalness
- 0 I don't criticize or blame myself more than usual.
- 1 I am more critical of myself than I used to be.
- 2 I criticize myself for all of my faults.
- 3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes
- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

10. Crying
- 0 I don't cry anymore than I used to.
- 1 I cry more than I used to.
- 2 I cry over every little thing.
- 3 I feel like crying, but I can't.

_____ Subtotal Page 1

Continued on Back

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11. Agitation

0 I am no more restless or wound up than usual.

1 I feel more restless or wound up than usual.

2 I am so restless or agitated that it's hard to stay still.

3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.

1 I am less interested in other people or things than before.

2 I have lost most of my interest in other people or things.

3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.

1 I find it more difficult to make decisions than usual.

2 I have much greater difficulty in making decisions than I used to.

3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.

1 I don't consider myself as worthwhile and useful as I used to.

2 I feel more worthless as compared to other people.

3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.

1 I have less energy than I used to have.

2 I don't have enough energy to do very much.

3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.

1a I sleep somewhat more than usual.

1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.

2b I sleep a lot less than usual.

3a I sleep most of the day.

3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.

1 I am more irritable than usual.

2 I am much more irritable than usual.

3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.

1a My appetite is somewhat less than usual.

1b My appetite is somewhat greater than usual.

2a My appetite is much less than before.

2b My appetite is much greater than usual.

3a I have no appetite at all.

3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.

1 I can't concentrate as well as usual.

2 It's hard to keep my mind on anything for very long.

3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.

1 I get more tired or fatigued more easily than usual.

2 I am too tired or fatigued to do a lot of the things I used to do.

3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I am much less interested in sex now.

3 I have lost interest in sex completely.

18 19 20 A B C D E

_____ Subtotal Page 2

_____ Subtotal Page 1

_____ Total Score

APPENDIX C: Connor's Adult ADHD Rating Scales

Instructions: Listed below are items concerning behaviors or problems sometimes experienced by adults. Read each item carefully and decide how much or how frequently each item describes you recently. Indicate your response for each item by circling the number that corresponds to your choice. Use the following scale: 0=Not at all, never; 1=Just a little, once in while; 2=Pretty much, often; 3=Very much, very frequently.	Not at all, never	Just a little, once in a while	Pretty much, often	Very much, very frequently
1. I like to be doing active things.	☐	☐	☐	☐
2. I lose things necessary for tasks or activities (e.g., to-do lists, pencil, books, or tools).	☐	☐	☐	☐
3. I don't plan ahead.	☐	☐	☐	☐
4. I blurt out things.	☐	☐	☐	☐
5. I am a risk-taker or a daredevil.	☐	☐	☐	☐
6. I get down on myself.	☐	☐	☐	☐
7. I don't finish things I start.	☐	☐	☐	☐
8. I am easily frustrated.	☐	☐	☐	☐
9. I talk too much.	☐	☐	☐	☐
10. I am always on the go, as if driven by a motor.	☐	☐	☐	☐
11. I'm disorganized.	☐	☐	☐	☐
12. I say things without thinking.	☐	☐	☐	☐
13. It's hard for me to stay in one place very long.	☐	☐	☐	☐
14. I have trouble doing leisure activities quietly.	☐	☐	☐	☐
15. I'm not sure of myself.	☐	☐	☐	☐
16. It's hard for me to keep track of several things at once.	☐	☐	☐	☐
17. I'm always moving even when I should be still.	☐	☐	☐	☐
18. I forget to remember things.	☐	☐	☐	☐
19. I have a short fuse/hot temper.	☐	☐	☐	☐
20. I'm bored easily.	☐	☐	☐	☐
21. I leave my seat when I am not supposed to.	☐	☐	☐	☐
22. I have trouble waiting in line or taking turns with others.	☐	☐	☐	☐
23. I still throw tantrums.	☐	☐	☐	☐
24. I have trouble keeping my attention focused when working.	☐	☐	☐	☐
25. I seek out fast paced, exciting activities.	☐	☐	☐	☐
26. I avoid new challenges because I lack faith in my abilities.	☐	☐	☐	☐
27. I feel restless inside even if I am sitting still.	☐	☐	☐	☐
28. Things I hear or see distract me from what I'm doing.	☐	☐	☐	☐

	Not at all, never	Just a little, once in a while	Pretty much, often	Very much, very frequently
29. I am forgetful in my daily activities.	☐	☐	☐	☐
30. Many things set me off easily.	☐	☐	☐	☐
31. I dislike quiet, introspective activities.	☐	☐	☐	☐
32. I lose things that I need.	☐	☐	☐	☐
33. I have trouble listening to what other people have to say.	☐	☐	☐	☐
34. I am an underachiever.	☐	☐	☐	☐
35. I interrupt others when talking.	☐	☐	☐	☐
36. I change plans/jobs in midstream.	☐	☐	☐	☐
37. I act okay on the outside, but inside I'm unsure of myself.	☐	☐	☐	☐
38. I am always on the go.	☐	☐	☐	☐
39. I make comments/remarks that I wish I could take back.	☐	☐	☐	☐
40. I can't get things done unless there's an absolute deadline.	☐	☐	☐	☐
41. I fidget (with my hands or feet) or squirm in my seat.	☐	☐	☐	☐
42. I make careless mistakes or have trouble paying close attention to detail.	☐	☐	☐	☐
43. I step on people's toes without meaning to.	☐	☐	☐	☐
44. I have trouble getting started on a task.	☐	☐	☐	☐
45. I intrude on others' activities.	☐	☐	☐	☐
46. It takes a great deal of effort for me to sit still.	☐	☐	☐	☐
47. My moods are unpredictable.	☐	☐	☐	☐
48. I don't like homework or job activities where I have to think alot.	☐	☐	☐	☐
49. I'm absent-minded in daily activities.	☐	☐	☐	☐
50. I am restless or overactive.	☐	☐	☐	☐
51. I depend on others to keep my life in order and attend to details.	☐	☐	☐	☐
52. I annoy other people without meaning to.	☐	☐	☐	☐
53. Sometimes my attention narrows so much that I'm oblivious to everything else, other times it's so broad that everything distracts me.	☐	☐	☐	☐
54. I tend to squirm or fidget.	☐	☐	☐	☐
55. I can't keep my mind on something unless it's really interesting.	☐	☐	☐	☐
56. I wish I had greater confidence in my abilities.	☐	☐	☐	☐
57. I can't sit still for very long.	☐	☐	☐	☐
58. I give answers to questions before the questions have been completed.	☐	☐	☐	☐
59. I like to be up and on the go rather than being in one place.	☐	☐	☐	☐

	Not at all, never	Just a little, once in a while	Pretty much, often	Very much, very frequently
60. I have trouble finishing job tasks or schoolwork.	☐	☐	☐	☐
61. I am irritable.	☐	☐	☐	☐
62. I interrupt others when they are working or playing.	☐	☐	☐	☐
63. My past failures make it hard for me to believe in myself.	☐	☐	☐	☐
64. I am distracted when things are going on around me.	☐	☐	☐	☐
65. I have problems organizing my tasks and activities.	☐	☐	☐	☐
66. I misjudge how long it takes to do something or go somewhere.	☐	☐	☐	☐

APPENDIX D: Clinician Administered PTSD Scale

National Center for PTSD

CLINICIAN-ADMINISTERED PTSD SCALE FOR DSM-5

PAST MONTH / WORST MONTH VERSION

Name: _____ ID#: _____

Interviewer: _____ Date: _____

Study: _____

Frank W. Weathers, Dudley D. Blake, Paula P. Schnurr,
Danny G. Kaloupek, Brian P. Marx, & Terence M. Keane

National Center for Posttraumatic Stress Disorder July 1, 2014

Instructions

Standard administration and scoring of the CAPS-5 are essential for producing reliable and valid scores and diagnostic decisions. The CAPS-5 should be administered only by qualified interviewers who have formal training in structured clinical interviewing and differential diagnosis, a thorough understanding of the conceptual basis of PTSD and its various symptoms, and detailed knowledge of the features and conventions of the CAPS-5 itself.

Administration

1. Identify an index traumatic event to serve as the basis for symptom inquiry. Administer the Life Events Checklist and Criterion A inquiry provided on p. 5, or use some other structured, evidence-based method. The index event may involve either a single incident (e.g., "the accident") or multiple, closely related incidents (e.g., "the worst parts of your combat experiences").

2. When assessing both past month (current) and worst month (lifetime):

    a. First, administer the time frame prompt which appears under the Criterion A assessment box. If the respondent reports that her/his symptoms have been as bad in the past month as they have been at any point since the index event, then the past month can also be considered the worst month. In that case there is no need to assess worst month; past month ratings will serve as the basis for both current and lifetime diagnostic status.

    b. Second, administer all items with respect to the past month and establish current diagnostic status.

    c. Third, if necessary, re-orient the respondent to the worst month time frame, and then re-administer all items with respect to worst month and establish lifetime diagnostic status. Rephrase prompts into past tense. For example, "have you had any unwanted memories" becomes "did you have any unwanted memories."

    d. Note: To assure comparability between past month ratings obtained from this version of the CAPS-5 and past month ratings obtained from the past month version of the CAPS-5, it is important to assess past month first, followed by worst month in a separate pass through the symptoms. It is recommended NOT to assess past month and worst month symptom by symptom in a single pass.

3. Read prompts verbatim, one at a time, and in the order presented, EXCEPT:

    a. Use the respondent's own words for labeling the index event or describing specific symptoms.

    b. Rephrase standard prompts to acknowledge previously reported information, but return to verbatim phrasing as soon as possible. For example, inquiry for item 20 might begin: "You already mentioned having problems sleeping. What kinds of problems?"

    c. If you don't have sufficient information after exhausting all standard prompts, follow up ad lib. In this situation, repeating the initial prompt often helps refocus the respondent.

    d. As needed, ask for specific examples or direct the respondent to elaborate even when such prompts are not provided explicitly.

4. In general, DO NOT suggest responses. If a respondent has pronounced difficulty understanding a prompt it may be necessary to offer a brief example to clarify and illustrate. However, this should be done rarely and only after the respondent has been given ample opportunity to answer spontaneously.

5. DO NOT read rating scale anchors to the respondent. They are intended only for you, the interviewer, because appropriate use requires clinical judgment and a thorough understanding of CAPS-5 scoring conventions

6. Move through the interview as efficiently as possible to minimize respondent burden. Some useful strategies:

a. Be thoroughly familiar with the CAPS-5 so that prompts flow smoothly.

b. Ask the fewest number of prompts needed to obtain sufficient information to support a valid rating.

c. Minimize note-taking and write while the respondent is talking to avoid long pauses.

d. Take charge of the interview. Be respectful but firm in keeping the respondent on task, transitioning between questions, pressing for examples, or pointing out contradictions.

Scoring

1. As with previous versions of the CAPS, CAPS-5 symptom severity ratings are based on symptom frequency and intensity, except for items 8 (amnesia) and 12 (diminished interest), which are based on amount and intensity. However, CAPS-5 items are rated with a single severity score, in contrast to previous versions of the CAPS which required separate frequency and intensity scores for each item that were either summed to create a symptom severity score or combined in various scoring rules to create a dichotomous (present/absent) symptom score. Thus, on the CAPS-5 the clinician combines information about frequency and intensity before making a single severity rating. Depending on the item, frequency is rated as either the number of occurrences (how often in the past month) or percent of time (how much of the time in the past month). Intensity is rated on a four-point ordinal scale with ratings of *Minimal*, *Clearly Present*, *Pronounced*, and *Extreme*. Intensity and severity are related but distinct. Intensity refers to the strength of a typical occurrence of a symptom. Severity refers to the total symptom load over a given time period, and is a combination of intensity and frequency. This is similar to the quantity/frequency assessment approach to alcohol consumption. In general, intensity rating anchors correspond to severity scale anchors described below and should be interpreted and used in the same way, except that severity ratings require joint consideration of intensity and frequency. Thus, before taking frequency into account, an intensity rating of *Minimal* corresponds to a severity rating of *Mild / subthreshold*, *Clearly Present* corresponds with *Moderate / threshold*, *Pronounced* corresponds with *Severe / markedly elevated*, and *Extreme* corresponds with *Extreme / incapacitating*.

2. The five-point CAPS-5 symptom severity rating scale is used for all symptoms. Rating scale anchors should be interpreted and used as follows:

0 ***Absent*** The respondent denied the problem or the respondent's report doesn't fit the DSM-5 symptom criterion.

1 ***Mild / subthreshold*** The respondent described a problem that is consistent with the symptom criterion but isn't severe enough to be considered clinically significant. The problem doesn't satisfy the DSM-5 symptom criterion and thus doesn't count toward a PTSD diagnosis.

2 ***Moderate / threshold*** The respondent described a clinically significant problem. The problem satisfies the DSM-5 symptom criterion and thus counts toward a PTSD diagnosis. The problem would be a target for intervention. This rating requires a minimum frequency of *2 X month* or *some of the time (20-30%)* PLUS a minimum intensity of *Clearly Present*.

3 ***Severe / markedly elevated*** The respondent described a problem that is well above threshold. The problem is difficult to manage and at times overwhelming, and would be a prominent target for intervention. This rating requires a minimum frequency of *2 X week* or *much of the time (50-60%)* PLUS a minimum intensity of *Pronounced*.

4 ***Extreme / incapacitating*** The respondent described a dramatic symptom, far above threshold. The problem is pervasive, unmanageable, and overwhelming, and would be a high-priority target for intervention.

3. In general, make a given severity rating only if the minimum frequency and intensity for that rating are both met. However, you may exercise clinical judgment in making a given severity rating if the reported frequency is somewhat lower than required, but the intensity is higher. For example, you may make a severity rating of *Moderate / threshold* if a symptom occurs *1 X month* (instead of the required *2 X month*) as long as intensity is rated *Pronounced* or *Extreme* (instead of the required *Clearly Present*). Similarly, you may make a severity rating of *Severe / markedly elevated* if a symptom occurs *1 X week* (instead of the required *2 X week*) as long as the intensity is rated *Extreme* (instead of the required *Pronounced*). If you are unable to decide between two severity ratings, make the lower rating.
4. You need to establish that a symptom not only meets the DSM-5 criterion phenomenologically, but is also functionally related to the index traumatic event, i.e., started or got worse as a result of the event. CAPS-5 items 1-8 and 10 (reexperiencing, effortful avoidance, amnesia, and blame) are inherently linked to the event. Evaluate the remaining items for trauma-relatedness (TR) using the TR inquiry and rating scale. The three TR ratings are:

    a. ***Definite*** = the symptom can clearly be attributed to the index trauma, because (1) there is an obvious change from the pre-trauma level of functioning and/or (2) the respondent makes the attribution to the index trauma with confidence.

    b. ***Probable*** **=** the symptom is likely related to the index trauma, but an unequivocal connection can't be made. Situations in which this rating would be given include the following: (1) there seems to be a change from the pre-trauma level of functioning, but it isn't as clear and explicit as it would be for a "definite;" (2) the respondent attributes a causal link between the symptom and the index trauma, but with less confidence than for a rating of *Definite*; (3) there appears to be a functional relationship between the symptom and inherently trauma-linked symptoms such as reexperiencing symptoms (e.g., numbing or withdrawal increases when reexperiencing increases).

    c. ***Unlikely*** = the symptom can be attributed to a cause other than the index trauma because (1) there is an obvious functional link with this other cause and/or (2) the respondent makes a confident attribution to this other cause and denies a link to the index trauma. Because it can be difficult to rule out a functional link between a symptom and the index trauma, a rating of *Unlikely* should be used only when the available evidence strongly points to a cause other than the index trauma. NOTE: Symptoms with a TR rating of *Unlikely* should not be counted toward a PTSD diagnosis or included in the total CAPS-5 symptom severity score.

5. **CAPS-5 total symptom severity score** is calculated by summing severity scores for items 1-20. NOTE: Severity scores for the two dissociation items (29 and 30) should NOT be included in the calculation of the total CAPS-5 severity score.

6. **CAPS-5 symptom cluster severity scores** are calculated by summing the individual item severity scores for symptoms contained in a given DSM-5 cluster. Thus, the Criterion B (reexperiencing) severity score is the sum of the individual severity scores for items 1-5; the Criterion C (avoidance) severity score is the sum of items 6 and 7; the Criterion D (negative alterations in cognitions and mood) severity score is the sum of items 8-14; and the Criterion E (hyperarousal) severity score is the sum of items 15-20. A symptom cluster score may also be calculated for dissociation by summing items 29 and 30.

7. **PTSD diagnostic status** is determined by first dichotomizing individual symptoms as "present" or "absent," then following the DSM-5 diagnostic rule. A symptom is considered present only if the corresponding item severity score is rated *2=Moderate/threshold* or higher. Items 9 and 11-20 have the additional requirement of a trauma-relatedness rating of *Definite* or *Probable*. Otherwise a symptom is considered absent. The DSM-5 diagnostic rule requires the presence of least one Criterion B symptom, one Criterion C symptom, two Criterion D symptoms, and two Criterion E symptoms. In addition, Criteria F and G must be met. Criterion F requires that the disturbance has lasted at least one month. Criterion G requires that the disturbance cause either clinically significant distress or functional impairment, as indicated by a rating of *2=moderate* or higher on items 23-25.

Criterion A: Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:

1. **Directly experiencing the traumatic event(s).**
2. **Witnessing, in person, the event(s) as it occurred to others.**
3. **Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.**
4. **Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse). Note: Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related.**

[Administer Life Events Checklist or other structured trauma screen]

I'm going to ask you about the stressful experiences questionnaire you filled out. First I'll ask you to tell me a little bit about the event you said was the worst for you. Then I'll ask how that event may have affected you. In general I don't need a lot of information – just enough so I can understand any problems you may have had.
Please let me know if you find yourself becoming upset as we go through the questions so we can slow down and talk about it. Also, let me know if you have any questions or don't understand something. Do you have any questions before we start?

The event you said was the worst was (EVENT). What I'd like for you to do is briefly describe what happened.

Index event (specify):

What happened? *(How old were you? How were you involved? Who else was involved? Was anyone seriously injured or killed? Was anyone's life in danger? How many times did this happen?)*	*Exposure type:* *Experienced ___* *Witnessed ___* *Learned about ___* *Exposed to aversive details___* *Life threat? NO YES [self ___ other ___]* *Serious injury? NO YES [self ___ other ___]* *Sexual violence? NO YES [self ___ other ___]* *Criterion A met? NO PROBABLE YES*

Since (EVENT) has there been a time when it was causing you more problems than it has over the past month? *[If yes:]* ***When was (EVENT) causing you the most problems?*** *[If not clear:]* ***Did it last at least a month?***

For the rest of the interview, I want you to keep (EVENT) in mind as I ask you about different problems it may have caused you. For this interview we're going to focus on the *[past month / worst month]***. For each problem I'll ask if you had it at all, and if so, how often and how much it bothered you.**

Criterion B: Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:

1. (B1) Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s). Note: In children older than 6 years, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.

In the *[past month / worst month]*, have you had any <u>unwanted memories</u> of (EVENT) while you were awake, so not counting dreams? [Rate 0=Absent if only during dreams] **How does it happen that you start remembering (EVENT)?** [If not clear:] ***(Are these <u>unwanted</u> memories, or are you thinking about [EVENT] on purpose?)*** [Rate 0=Absent unless perceived as involuntary and intrusive] **How much do these memories bother you?** **Are you able to put them out of your mind and think about something else?** <u>Circle</u>: Distress = *Minimal Clearly Present Pronounced Extreme* **How often have you had these memories in the *[past month / worst month]*?** *# times* _____ ***Key rating dimensions = frequency / intensity of distress*** Moderate = at least 2 X month / distress clearly present, some difficulty dismissing memories Severe = at least 2 X week / pronounced distress, considerable difficulty dismissing memories	**0 *Absent*** **1 *Mild / subthreshold*** **2 *Moderate / threshold*** **3 *Severe / markedly elevated*** **4 *Extreme / incapacitating*** Past month _____ Worst month _____

2. (B2) Recurrent distressing dreams in which the content and/or affect of the dream are related to the event(s). Note: In children, there may be frightening dreams without recognizable content.

In the *[past month / worst month]*, have you had any <u>unpleasant dreams</u> about (EVENT)? **Describe a typical dream.** *(What happens?)* [If not clear:] ***(Do they wake you up?)*** [If yes:] ***(What do you experience when you wake up? How long does it take you to get back to sleep?)*** [If reports not returning to sleep:] ***(How much sleep do you lose?)*** **How much do these dreams bother you?** <u>Circle</u>: Distress = *Minimal Clearly Present Pronounced Extreme* **How often have you had these dreams in the *[past month / worst month]*?** *# of times* _____ ***Key rating dimensions = frequency / intensity of distress*** Moderate = at least 2 X month / distress clearly present, less than 1 hour sleep loss Severe = at least 2 X week / pronounced distress, more than 1 hour sleep loss	**0 *Absent*** **1 *Mild / subthreshold*** **2 *Moderate / threshold*** **3 *Severe / markedly elevated*** **4 *Extreme / incapacitating*** Past month _____ Worst month _____

3. (B3) Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.) Note: In children, trauma-specific reenactment may occur in play.

In the *[past month / worst month]*, have there been times when you <u>suddenly acted</u> or <u>felt</u> as if (EVENT) were <u>actually happening</u> again? [If not clear:] ***(This is different than thinking about it or dreaming about it – now I'm asking about flashbacks, when you feel like you're actually back at the time of [EVENT], actually reliving it.)*** **How much does it seem as if (EVENT) were happening again?** *(Are you confused about where you actually are?)* **What do you do while this is happening?** *(Do other people notice your behavior? What do they say?)* **How long does it last?** <u>Circle</u>: Dissociation = *Minimal Clearly Present Pronounced Extreme* **How often has this happened in the *[past month / worst month]*?** *# of times* _____ ***Key rating dimensions = frequency / intensity of dissociation*** Moderate = at least 2 X month / dissociative quality clearly present, may retain some awareness of surroundings but relives event in a manner clearly distinct from thoughts and memories Severe = at least 2 X week / pronounced dissociative quality, reports vivid reliving, e.g., with images, sounds, smells	**0 *Absent*** **1 *Mild / subthreshold*** **2 *Moderate / threshold*** **3 *Severe / markedly elevated*** **4 *Extreme / incapacitating*** Past month _____ Worst month _____

4. (B4) Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

In the *[past month / worst month]*, have you gotten <u>emotionally upset</u> when <u>something reminded you</u> of (EVENT)? **What kinds of reminders make you upset?** **How much do these reminders bother you?** **Are you able to calm yourself down when this happens?** *(How long does it take?)* <u>Circle</u>: Distress = *Minimal Clearly Present Pronounced Extreme* **How often has this happened in the *[past month / worst month]*?** *# of times* _____ ***Key rating dimensions = frequency / intensity of distress*** Moderate = at least 2 X month / distress clearly present, some difficulty recovering Severe = at least 2 X week / pronounced distress, considerable difficulty recovering	**0 *Absent*** **1 *Mild / subthreshold*** **2 *Moderate / threshold*** **3 *Severe / markedly elevated*** **4 *Extreme / incapacitating*** Past month _____ Worst month _____

5. (B5) Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

In the *[past month / worst month]*, have you had any <u>physical reactions</u> when <u>something reminded you</u> of (EVENT)? **Can you give me some examples?** *(Does your heart race or your breathing change? What about sweating or feeling really tense or shaky?)* **What kinds of reminders trigger these reactions?** **How long does it take you to recover?** <u>Circle</u>: Physiological reactivity = *Minimal Clearly Present Pronounced Extreme* **How often has this happened in the *[past month / worst month]*?** *# of times* _____ ***Key rating dimensions = frequency / intensity of physiological arousal*** Moderate = at least 2 X month / reactivity clearly present, some difficulty recovering Severe = at least 2 X week / pronounced reactivity, sustained arousal, considerable difficulty recovering	**0 *Absent*** **1 *Mild / subthreshold*** **2 *Moderate / threshold*** **3 *Severe / markedly elevated*** **4 *Extreme / incapacitating*** Past month _____ Worst month _____

Criterion C: Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:

6. (C1) Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

In the *[past month / worst month]*, have you tried to <u>avoid thoughts</u> or <u>feelings</u> about (EVENT)? **What kinds of thoughts or feelings do you avoid?** **How hard do you try to avoid these thoughts or feelings?** *(What kinds of things do you do?)* <u>Circle</u>: Avoidance = *Minimal Clearly Present Pronounced Extreme* **How often in the *[past month / worst month]*?** *# of times* _____ ***Key rating dimensions = frequency / intensity of avoidance*** Moderate = at least 2 X month / avoidance clearly present Severe = at least 2 X week / pronounced avoidance	**0 *Absent*** **1 *Mild / subthreshold*** **2 *Moderate / threshold*** **3 *Severe / markedly elevated*** **4 *Extreme / incapacitating*** Past month _____ Worst month _____

7. (C2) Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

In the *[past month / worst month]*, have you tried to <u>avoid things</u> that <u>remind you</u> of (EVENT), like certain people, places, or situations? **What kinds of things do you avoid?** **How much effort do you make to avoid these reminders?** *(Do you have to make a plan or change your activities to avoid them?)* [If not clear:] ***(Overall, how much of a problem is this for you? How would things be different if you didn't have to avoid these reminders?)*** <u>Circle</u>: Avoidance = *Minimal Clearly Present Pronounced Extreme* **How often in the *[past month / worst month]*?** *# of times* _____ ***Key rating dimensions = frequency / intensity of avoidance*** Moderate = at least 2 X month / avoidance clearly present Severe = at least 2 X week / pronounced avoidance	**0 *Absent*** **1 *Mild / subthreshold*** **2 *Moderate / threshold*** **3 *Severe / markedly elevated*** **4 *Extreme / incapacitating*** Past month _____ Worst month _____

Criterion D: Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:

8. (D1) Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).

In the *[past month / worst month]*, have you had <u>difficulty remembering</u> some <u>important parts</u> of (EVENT)? *(Do you feel there are gaps in your memory of [EVENT]?)* **What parts have you had difficulty remembering?** **Do you feel you should be able to remember these things?** [If not clear:] ***(Why do you think you can't? Did you have a head injury during [EVENT]? Were you knocked unconscious? Were you intoxicated from alcohol or drugs?)*** [Rate 0=Absent if due to head injury or loss of consciousness or intoxication during event] [If still not clear:] ***(Is this just normal forgetting? Or do you think you may have blocked it out because it would be too painful to remember?)*** [Rate 0=Absent if due only to normal forgetting] <u>Circle</u>: Difficulty remembering = *Minimal Clearly Present Pronounced Extreme* **In the *[past month / worst month]*, how many of the important parts of (EVENT) have you**	**0 *Absent*** **1 *Mild / subthreshold*** **2 *Moderate / threshold*** **3 *Severe / markedly elevated*** **4 *Extreme / incapacitating*** Past month _____ Worst month _____

had difficulty remembering? *(What parts do you still remember?)* *# of aspects* _____

Would you be able to recall these things if you tried?

Key rating dimensions = amount of event not recalled / intensity of inability to recall
Moderate = at least one important aspect / difficulty remembering clearly present, some recall possible with effort

9. (D2) Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., “I am bad,” “No one can be trusted,” “The world is completely dangerous,” “My whole nervous system is permanently ruined”).

In the *[past month / worst month]*, have you had <u>strong negative beliefs</u> about yourself, other people, or the world? **Can you give me some examples?** *(What about believing things like “I am bad,” “there is something seriously wrong with me,” “no one can be trusted,” “the world is completely dangerous”?)* **How strong are these beliefs?** *(How convinced are you that these beliefs are actually true? Can you see other ways of thinking about it?)* <u>Circle</u>: Conviction = *Minimal Clearly Present Pronounced Extreme* **How much of the time in the *[past month / worst month]* have you felt that way?** *% of time* _____ **Did these beliefs start or get worse after (EVENT)?** *(Do you think they’re related to [EVENT]? How so?)* <u>Circle</u>: Trauma-relatedness = *Definite Probable Unlikely* ***Key rating dimensions = frequency / intensity of beliefs*** Moderate = some of the time (20-30%) / exaggerated negative expectations clearly present, some difficulty considering more realistic beliefs Severe = much of the time (50-60%) / pronounced exaggerated negative expectations, considerable difficulty considering more realistic beliefs	**0 *Absent*** **1 *Mild / subthreshold*** **2 *Moderate / threshold*** **3 *Severe / markedly elevated*** **4 *Extreme / incapacitating*** Past month _____ Worst month _____

10. (D3) Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.

In the *[past month / worst month]*, have you <u>blamed yourself</u> for (EVENT) or what happened as a result of it? Tell me more about that. *(In what sense do you see yourself as having caused [EVENT]? Is it because of something you did? Or something you think you should have done but didn’t? Is it because of something about you in general?)* **What about <u>blaming someone else</u> for (EVENT) or what happened as a result of it? Tell me more about that.** *(In what sense do you see [OTHERS] as having caused [EVENT]? Is it because of something they did? Or something you think they should have done but didn’t?)* **How much do you blame (YOURSELF OR OTHERS)?** **How convinced are you that [YOU OR OTHERS] are truly responsible for what happened?** *(Do other people agree with you? Can you see other ways of thinking about it?)* [Rate 0=Absent if only blames perpetrator, i.e., someone who deliberately caused the event and intended harm] <u>Circle</u>: Conviction = *Minimal Clearly Present Pronounced Extreme* **How much of the time in the *[past month / worst month]* have you felt that way?** *% of time* _____ ***Key rating dimensions = frequency / intensity of blame*** Moderate = some of the time (20-30%) / distorted blame clearly present, some difficulty considering more realistic	**0 *Absent*** **1 *Mild / subthreshold*** **2 *Moderate / threshold*** **3 *Severe / markedly elevated*** **4 *Extreme / incapacitating*** Past month _____ Worst month _____

11. (D4) Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).

In the *[past month / worst month]*, have you had any <u>strong negative feelings</u> such as fear, horror, anger, guilt, or shame? **Can you give me some examples?** *(What negative feelings do you experience?)* **How strong are these negative feelings?** **How well are you able to manage them?** <u>Circle</u>: Negative emotions = *Minimal Clearly Present Pronounced Extreme* **How much of the time in the *[past month / worst month]* have you felt that way?** % *of time* _____ **Did these negative feelings start or get worse after (EVENT)?** *(Do you think they're related to [EVENT]? How so?)* <u>Circle</u>: Trauma-relatedness = *Definite Probable Unlikely* ***Key rating dimensions = frequency / intensity of negative emotions*** Moderate = some of the time (20-30%) / negative emotions clearly present, some difficulty managing Severe = much of the time (50-60%) / pronounced negative emotions, considerable difficulty managing	**0 *Absent*** **1 *Mild / subthreshold*** **2 *Moderate / threshold*** **3 *Severe / markedly elevated*** **4 *Extreme / incapacitating*** Past month _____ Worst month _____

12. (D5) Markedly diminished interest or participation in significant activities.

In the *[past month / worst month]*, have you been <u>less interested</u> in <u>activities</u> that you used to enjoy? **What kinds of things have you lost interest in or don't do as much as you used to?** *(Anything else?)* **Why is that?** [Rate 0=Absent if diminished participation is due to lack of opportunity, physical inability, or developmentally appropriate change in preferred activities] **How strong is your loss of interest?** *(Would you still enjoy [ACTIVITIES] once you got started?)* <u>Circle</u>: Loss of interest= *Minimal Clearly Present Pronounced Extreme* **Overall, in the *[past month / worst month]*, how many of your usual activities have you been less interested in?** % *of activities* _____ **What kinds of things do you still enjoy doing?** **Did this loss of interest start or get worse after (EVENT)?** *(Do you think it's related to [EVENT]? How so?)* <u>Circle</u>: Trauma-relatedness = *Definite Probable Unlikely* ***Key rating dimensions = percent of activities affected / intensity of loss of interest*** Moderate = some activities (20-30%) / loss of interest clearly present but still has some enjoyment of activities	**0 *Absent*** **1 *Mild / subthreshold*** **2 *Moderate / threshold*** **3 *Severe / markedly elevated*** **4 *Extreme / incapacitating*** Past month _____ Worst month _____

Severe = many activities (50-60%) / pronounced loss of interest, little interest or participation in activities	

13. (D6) Feelings of detachment or estrangement from others.

In the *[past month / worst month]*, have you felt <u>distant</u> or <u>cut off</u> from other people? **Tell me more about that.** **How strong are your feelings of being distant or cut off from others?** *(Who do you feel closest to? How many people do you feel comfortable talking with about personal things?)* <u>Circle</u>: Detachment or estrangement = *Minimal Clearly Present Pronounced Extreme* **How much of the time in the *[past month / worst month]* have you felt that way?** *% of time* _____ **Did this feeling of being distant or cut off start or get worse after (EVENT)?** *(Do you think it's related to [EVENT]? How so?)* <u>Circle</u>: Trauma-relatedness = *Definite Probable Unlikely* ***Key rating dimensions = frequency / intensity of detachment or estrangement*** Moderate = some of the time (20-30%) / feelings of detachment clearly present but still feels some interpersonal connection Severe = much of the time (50-60%) / pronounced feelings of detachment or estrangement from most people, may feel close to only one or two people	**0 *Absent*** **1 *Mild / subthreshold*** **2 *Moderate / threshold*** **3 *Severe / markedly elevated*** **4 *Extreme / incapacitating*** Past month _____ Worst month _____

14. (D7) Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).

In the *[past month / worst month]*, have there been times when you had <u>difficulty experiencing positive feelings</u> like love or happiness? **Tell me more about that.** *(What feelings are difficult to experience?)* **How much difficulty do you have experiencing positive feelings?** *(Are you still able to experience any positive feelings?)* <u>Circle</u>: Reduction of positive emotions = *Minimal Clearly Present Pronounced Extreme* **How much of the time in the *[past month / worst month]* have you felt that way?** *% of time* _____ **Did this trouble experiencing positive feelings start or get worse after (EVENT)?** *(Do you think it's related to [EVENT]? How so?)* <u>Circle</u>: Trauma-relatedness = *Definite Probable Unlikely* ***Key rating dimensions = frequency / intensity of reduction in positive emotions*** Moderate = some of the time (20-30%) / reduction of positive emotional experience clearly present but still able to experience some positive emotions Severe = much of the time (50-60%) / pronounced reduction of experience across range of positive emotions	**0 *Absent*** **1 *Mild / subthreshold*** **2 *Moderate / threshold*** **3 *Severe / markedly elevated*** **4 *Extreme / incapacitating*** Past month _____ Worst month _____

Criterion E: Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:

15. (E1) Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects.

In the *[past month / worst month]*, have there been times when you felt especially irritable or angry and showed it in your behavior? **Can you give me some examples?** *(How do you show it? Do you raise your voice or yell? Throw or hit things? Push or hit other people?)* Circle: Aggression = *Minimal Clearly Present Pronounced Extreme* **How often in the *[past month / worst month]*?** *# of times* _____ **Did this behavior start or get worse after (EVENT)?** *(Do you think it's related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite Probable Unlikely* ***Key rating dimensions = frequency / intensity of aggressive behavior*** Moderate = at least 2 X month / aggression clearly present, primarily verbal Severe = at least 2 X week / pronounced aggression, at least some physical aggression	**0 *Absent*** **1 *Mild / subthreshold*** **2 *Moderate / threshold*** **3 *Severe / markedly elevated*** **4 *Extreme / incapacitating*** Past month _____ Worst month _____

16. (E2) Reckless or self-destructive behavior.

In the *[past month / worst month]*, have there been times when you were taking more risks or doing things that might have caused you harm? **Can you give me some examples?** **How much of a risk do you take?** *(How dangerous are these behaviors? Were you injured or harmed in some way?)* Circle: Risk = *Minimal Clearly Present Pronounced Extreme* **How often have you taken these kinds of risks in the *[past month / worst month]*?** *# of times* _____ **Did this behavior start or get worse after (EVENT)?** *(Do you think it's related to [EVENT]? How so?)* Circle: Trauma-relatedness = *Definite Probable Unlikely* ***Key rating dimensions = frequency / degree of risk*** Moderate = at least 2 X month / risk clearly present, may have been harmed Severe = at least 2 X week / pronounced risk, actual harm or high probability of harm	**0 *Absent*** **1 *Mild / subthreshold*** **2 *Moderate / threshold*** **3 *Severe / markedly elevated*** **4 *Extreme / incapacitating*** Past month _____ Worst month _____

17. (E3) Hypervigilance.

In the *[past month / worst month]*, have you been especially <u>alert</u> or <u>watchful</u>, even when there was no specific threat or danger? *(Have you felt as if you had to be on guard?)* **Can you give me some examples?** *(What kinds of things do you do when you're alert or watchful?)* [If not clear:] ***(What causes you to react this way? Do you feel like you're in danger or threatened in some way? Do you feel that way more than most people would in the same situation?)*** <u>Circle</u>: Hypervigilance = *Minimal Clearly Present Pronounced Extreme* **How much of the time in the *[past month / worst month]* have you felt that way?** % *of time* _____ **Did being especially alert or watchful start or get worse after (EVENT)?** *(Do you think it's related to [EVENT]? How so?)* <u>Circle</u>: Trauma-relatedness = *Definite Probable Unlikely* ***Key rating dimensions = frequency / intensity of hypervigilance*** Moderate = some of the time (20-30%) / hypervigilance clearly present, e.g., watchful in public, heightened awareness of threat Severe = much of the time (50-60%) / pronounced hypervigilance, e.g., scans environment for danger, may have safety rituals, exaggerated concern for safety of self/family/home	**0 *Absent*** **1 *Mild / subthreshold*** **2 *Moderate / threshold*** **3 *Severe / markedly elevated*** **4 *Extreme / incapacitating*** Past month _____ Worst month _____

18. (E4) Exaggerated startle response.

In the *[past month / worst month]*, have you had any <u>strong startle</u> reactions? **What kinds of things made you startle?** **How strong are these startle reactions?** *(How strong are they compared to how most people would respond? Do you do anything other people would notice?)* **How long does it take you to recover?** <u>Circle</u>: Startle = *Minimal Clearly Present Pronounced Extreme* **How often has this happened in the *[past month / worst month]*?** *# of times* _____ **Did these startle reactions start or get worse after (EVENT)?** *(Do you think they're related to [EVENT]? How so?)* <u>Circle</u>: Trauma-relatedness = *Definite Probable Unlikely* ***Key rating dimensions = frequency / intensity of startle*** Moderate = at least 2 X month / startle clearly present, some difficulty recovering Severe = at least 2 X week / pronounced startle, sustained arousal, considerable difficulty recovering	**0 *Absent*** **1 *Mild / subthreshold*** **2 *Moderate / threshold*** **3 *Severe / markedly elevated*** **4 *Extreme / incapacitating*** Past month _____ Worst month _____

19. (E5) Problems with concentration.

In the *[past month / worst month]*, have you had any <u>problems</u> with <u>concentration</u>? **Can you give me some examples?** **Are you able to concentrate if you really try?** <u>Circle</u>: Problem concentrating = *Minimal Clearly Present Pronounced Extreme* **How much of the time in the *[past month / worst month]* have you had problems with concentration?** *% of time* _____ **Did these problems with concentration start or get worse after (EVENT)?** *(Do you think they're related to [EVENT]? How so?)* <u>Circle</u>: Trauma-relatedness = *Definite Probable Unlikely* ***Key rating dimensions = frequency / intensity of concentration problems*** Moderate = some of the time (20-30%) / problem concentrating clearly present, some difficulty but can concentrate with effort Severe = much of the time (50-60%) / pronounced problem concentrating, considerable difficulty even with effort	**0 *Absent*** **1 *Mild / subthreshold*** **2 *Moderate / threshold*** **3 *Severe / markedly elevated*** **4 *Extreme / incapacitating*** Past month _____ Worst month _____

20. (E6) Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).

In the *[past month / worst month]*, have you had any problems <u>falling</u> or <u>staying</u> asleep? **What kinds of problems?** *(How long does it take you to fall asleep? How often do you wake up in the night? Do you wake up earlier than you want to?)* **How many total hours do you sleep each night?** **How many hours do you think you should be sleeping?** <u>Circle</u>: Problem sleeping = *Minimal Clearly Present Pronounced Extreme* **How often in the *[past month / worst month]* have you had these sleep problems?** *# of times* _____ **Did these sleep problems start or get worse after (EVENT)?** *(Do you think they're related to [EVENT]? How so?)* <u>Circle</u>: Trauma-relatedness = *Definite Probable Unlikely* ***Key rating dimensions = frequency / intensity of sleep problems*** Moderate = at least 2 X month / sleep disturbance clearly present, clearly longer latency or clear difficulty staying asleep, 30-90 minutes loss of sleep Severe = at least 2 X week / pronounced sleep disturbance, considerably longer latency or marked difficulty staying asleep, 90 min to 3 hrs loss of sleep	**0 *Absent*** **1 *Mild / subthreshold*** **2 *Moderate / threshold*** **3 *Severe / markedly elevated*** **4 *Extreme / incapacitating*** Past month _____ Worst month _____

Criterion F: Duration of the disturbance (Criteria B, C, D, and E) is more than 1 month.

21. Onset of symptoms

[If not clear:] **When did you first start having (PTSD SYMPTOMS) you've told me about?** *(How long after the trauma did they start? More than six months?)*	***Total # months delay in onset*** _____ ***With delayed onset (≥ 6 months)? NO YES***

22. Duration of symptoms

[If not clear:] **How long have these (PTSD SYMPTOMS) lasted altogether?**	***Total # months duration*** _____ ***Duration more than 1 month? NO YES***

Criterion G: The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

23. Subjective distress

Overall, in the *[past month / worst month]*, how much have you been bothered by these (PTSD SYMPTOMS) you've told me about? [Consider distress reported on earlier items]	**0** ***None*** **1** ***Mild, minimal distress*** **2** ***Moderate, distress clearly present but still manageable*** **3** ***Severe, considerable distress*** **4** ***Extreme, incapacitating distress*** Past month _____ Worst month _____

24. Impairment in social functioning

In the *[past month / worst month]*, have these (PTSD SYMPTOMS) affected your relationships with other people? How so? [Consider impairment in social functioning reported on earlier items]	**0** ***No adverse impact*** **1** ***Mild impact, minimal impairment in social functioning*** **2** ***Moderate impact, definite impairment but many aspects of social functioning still intact*** **3** ***Severe impact, marked impairment, few aspects of social functioning still intact*** **4** ***Extreme impact, little or no social functioning*** Past month _____ Worst month _____

25. Impairment in occupational or other important area of functioning

[If not clear:] **Are you working now?** [If yes:] **In the *[past month / worst month]*, have these (PTSD SYMPTOMS) affected your work or your ability to work? How so?** [Consider reported work history, including number and duration of jobs, as well as the quality of work relationships. If premorbid functioning is unclear, inquire about work experiences before the trauma. For child/adolescent trauma, assess pre-trauma school performance and possible presence of behavior problems] [If no:] **Have these (PTSD SYMPTOMS) affected any other important part of your life?** [As appropriate, suggest examples such as parenting, housework, schoolwork, volunteer work, etc.] **How so?**	**0** ***No adverse impact*** **1** ***Mild impact, minimal impairment in occupational/other important functioning*** **2** ***Moderate impact, definite impairment but many aspects of occupational/other important functioning still intact*** **3** ***Severe impact, marked impairment, few aspects of occupational/other important functioning still intact*** **4** ***Extreme impact, little or no occupational/other important functioning*** Past month _____ Worst month _____

Global Ratings

26. Global validity

Estimate the overall validity of responses. Consider factors such as compliance with the interview, mental status (e.g., problems with concentration, comprehension of items, dissociation), and evidence of efforts to exaggerate or minimize symptoms.	**0** ***Excellent, no reason to suspect invalid responses*** **1** ***Good, factors present that may adversely affect validity*** **2** ***Fair, factors present that definitely reduce validity*** **3** ***Poor, substantially reduced validity*** **4** ***Invalid responses, severely impaired mental status or possible deliberate "faking bad" or "faking good"*** Past month _____ Worst month _____

27. Global severity

Estimate the overall severity of PTSD symptoms. Consider degree of subjective distress, degree of functional impairment, observations of behaviors in interview, and judgment regarding reporting style.	**0** ***No clinically significant symptoms, no distress and no functional impairment*** **1** ***Mild, minimal distress or functional impairment*** **2** ***Moderate, definite distress or functional impairment but functions satisfactorily with effort*** **3** ***Severe, considerable distress or functional impairment, limited functioning even with effort*** **4** ***Extreme, marked distress or marked impairment in two or more major areas of functioning*** Past month _____ Worst month _____

28. Global improvement

Rate total overall improvement since the previous rating. Rate the degree of change, whether or not, in your judgment, it is due to treatment.	**0** ***Asymptomatic*** **1** ***Considerable improvement*** **2** ***Moderate improvement*** **3** ***Slight improvement*** **4** ***No improvement*** **5** ***Insufficient information***

Specify whether with dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder, and in addition, in response to the stressor, the individual experiences persistent or recurrent symptoms of either of the following:

29. (1) Depersonalization: Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).

In the *[past month / worst month]*, have there been times when you felt as if you were separated from yourself, like you were watching yourself from the outside or observing your thoughts and feelings as if you were another person?

[If no:] ***(What about feeling as if you were in a dream, even though you were awake? Feeling as if something about you wasn't real? Feeling as if time was moving more slowly?)***

Tell me more about that.

How strong is this feeling? *(Do you lose track of where you actually are or what's actually going on?)*

What do you do while this is happening? *(Do other people notice your behavior? What do they say?)*

How long does it last?

Circle: Dissociation = *Minimal Clearly Present Pronounced Extreme*

[If not clear:] ***(Was this due to the effects of alcohol or drugs? What about a medical condition like seizures?)*** [Rate 0=Absent if due to the effects of a substance or another medical condition]

How often has this happened in the *[past month / worst month]*? *# of times* _____

Key rating dimensions = frequency / intensity of dissociation
Moderate = at least 2 X month / dissociative quality clearly present but transient, retains some realistic sense of self and awareness of environment
Severe = at least 2 X week / pronounced dissociative quality, marked sense of detachment and unreality

0 ***Absent***

1 ***Mild / subthreshold***

2 ***Moderate / threshold***

3 ***Severe / markedly elevated***

4 ***Extreme / incapacitating***

Past month _____

Worst month _____

30. (2) Derealization: Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).

In the *[past month / worst month]*, have there been times when things going on around you seemed unreal or very strange and unfamiliar?

[If no:] ***(Do things going on around you seem like a dream or like a scene from a movie? Do they seem distant or distorted?)***

Tell me more about that.

How strong is this feeling? *(Do you lose track of where you actually are or what's actually going on?)*

What do you do while this is happening? *(Do other people notice your behavior? What do they say?)*

How long does it last?

Circle: Dissociation = *Minimal Clearly Present Pronounced Extreme*

[If not clear:] ***(Was this due to the effects of alcohol or drugs? What about a medical condition like seizures?)*** [Rate 0=Absent if due to the effects of a substance or another medical condition]

How often has this happened in the *[past month / worst month]*? *# of times* _____

Key rating dimensions = frequency / intensity of dissociation
Moderate = at least 2 X month / dissociative quality clearly present but transient, retains some realistic sense of environment
Severe = at least 2 X week / pronounced dissociative quality, marked sense of unreality

0 *Absent*

1 *Mild / subthreshold*

2 *Moderate / threshold*

3 *Severe / markedly elevated*

4 *Extreme / incapacitating*

Past month _____

Worst month _____

CAPS-5 SUMMARY SHEET

Name:_____ ID#:_____ Interviewer:_____ Study:_____
Date:_____

A. Exposure to actual or threatened death, serious injury, or sexual violence	
Criterion A met?	**0 = NO 1 = YES**

PAST MONTH RATINGS:

B. Intrusion symptoms (need 1 for diagnosis)		*Past Month*
	Sev	***Sx (Sev ≥ 2)?***
(1) B1 – Intrusive memories		**0 = NO 1 = YES**
(2) B2 – Distressing dreams		**0 = NO 1 = YES**
(3) B3 – Dissociative reactions		**0 = NO 1 = YES**
(4) B4 – Cued psychological distress		**0 = NO 1 = YES**
(5) B5 – Cued physiological reactions		**0 = NO 1 = YES**
B subtotals	***B Sev =***	***# B Sx =***

C. Avoidance symptoms (need 1 for diagnosis)		*Past Month*
	Sev	***Sx (Sev ≥ 2)?***
(6) C1 – Avoidance of memories, thoughts, feelings		**0 = NO 1 = YES**
(7) C2 – Avoidance of external reminders		**0 = NO 1 = YES**
C subtotals	***C Sev =***	***# C Sx =***

D. Cognitions and mood symptoms (need 2 for diagnosis)		*Past Month*
	Sev	***Sx (Sev ≥ 2)?***
(8) D1 – Inability to recall important aspect of event		**0 = NO 1 = YES**
(9) D2 – Exaggerated negative beliefs or expectations		**0 = NO 1 = YES**
(10) D3 – Distorted cognitions leading to blame		**0 = NO 1 = YES**
(11) D4 – Persistent negative emotional state		**0 = NO 1 = YES**
(12) D5 – Diminished interest or participation in activities		**0 = NO 1 = YES**
(13) D6 – Detachment or estrangement from others		**0 = NO 1 = YES**
(14) D7 – Persistent inability to experience positive emotions		**0 = NO 1 = YES**
D subtotals	***D Sev =***	***# D Sx =***

E. Arousal and reactivity symptoms (need 2 for diagnosis)		*Past Month*
	Sev	***Sx (Sev ≥ 2)?***
(15) E1 – Irritable behavior and angry outbursts		**0 = NO 1 = YES**
(16) E2 – Reckless or self-destructive behavior		**0 = NO 1 = YES**
(17) E3 – Hypervigilance		**0 = NO 1 = YES**
(18) E4 – Exaggerated startle response		**0 = NO 1 = YES**

(19) E5 – Problems with concentration		**0 = NO 1 = YES**
(20) E6 – Sleep disturbance		**0 = NO 1 = YES**
E subtotals	***E Sev =***	***# E Sx =***

PTSD totals		*Past Month*
	Total Sev	*Total # Sx*
Sum of subtotals (B+C+D+E)		

F. Duration of disturbance	*Current*
(22) Duration of disturbance ≥ 1 month?	**0 = NO 1 = YES**

G. Distress or impairment (need 1 for diagnosis)		*Past Month*
	Sev	*Cx (Sev ≥ 2)?*
(23) Subjective distress		**0 = NO 1 = YES**
(24) Impairment in social functioning		**0 = NO 1 = YES**
(25) Impairment in occupational functioning		**0 = NO 1 = YES**
G subtotals	*G Sev =*	*# G Cx =*

Global ratings	*Past Month*
(26) Global validity	
(27) Global severity	
(28) Global improvement	

Dissociative symptoms (need 1 for subtype)		*Past Month*
	Sev	*Sx (Sev ≥ 2)?*
(29) 1 -- Depersonalization		**0 = NO 1 = YES**
(30) 2 – Derealization		**0 = NO 1 = YES**
Dissociative subtotals	*Diss Sev =*	*# Diss Sx =*

PTSD diagnosis	*Past Month*
PTSD PRESENT – ALL CRITERIA (A-G) MET?	**0 = NO 1 = YES**
With dissociative symptoms	**0 = NO 1 = YES**
(21) With delayed onset (≥ 6 months)	**0 = NO 1 = YES**

WORST MONTH RATINGS:

B. Intrusion symptoms (need 1 for diagnosis)		*Worst Month*
	Sev	*Sx (Sev ≥ 2)?*
(1) B1 – Intrusive memories		**0 = NO 1 = YES**
(2) B2 – Distressing dreams		**0 = NO 1 = YES**
(3) B3 – Dissociative reactions		**0 = NO 1 = YES**
(4) B4 – Cued psychological distress		**0 = NO 1 = YES**
(5) B5 – Cued physiological reactions		**0 = NO 1 = YES**
B subtotals	*B Sev =*	*# B Sx =*

C. Avoidance symptoms (need 1 for diagnosis)		*Worst Month*
	Sev	*Sx (Sev ≥ 2)?*
(6) C1 – Avoidance of memories, thoughts, feelings		**0 = NO 1 = YES**
(7) C2 – Avoidance of external reminders		**0 = NO 1 = YES**
C subtotals	***C Sev =***	***# C Sx =***

D. Cognitions and mood symptoms (need 2 for diagnosis)		*Worst Month*
	Sev	*Sx (Sev ≥ 2)?*
(8) D1 – Inability to recall important aspect of event		**0 = NO 1 = YES**
(9) D2 – Exaggerated negative beliefs or expectations		**0 = NO 1 = YES**
(10) D3 – Distorted cognitions leading to blame		**0 = NO 1 = YES**
(11) D4 – Persistent negative emotional state		**0 = NO 1 = YES**
(12) D5 – Diminished interest or participation in activities		**0 = NO 1 = YES**
(13) D6 – Detachment or estrangement from others		**0 = NO 1 = YES**
(14) D7 – Persistent inability to experience positive emotions		**0 = NO 1 = YES**
D subtotals	***D Sev =***	***# D Sx =***

E. Arousal and reactivity symptoms (need 2 for diagnosis)		*Worst Month*
	Sev	*Sx (Sev ≥ 2)?*
(15) E1 – Irritable behavior and angry outbursts		**0 = NO 1 = YES**
(16) E2 – Reckless or self-destructive behavior		**0 = NO 1 = YES**
(17) E3 – Hypervigilance		**0 = NO 1 = YES**
(18) E4 – Exaggerated startle response		**0 = NO 1 = YES**
(19) E5 – Problems with concentration		**0 = NO 1 = YES**
(20) E6 – Sleep disturbance		**0 = NO 1 = YES**
E subtotals	***E Sev =***	***# E Sx =***

PTSD totals	*Worst Month*	
	Total Sev	*Total # Sx*
Sum of subtotals (B+C+D+E)		

F. Duration of disturbance	*Lifetime*
(22) Duration of disturbance ≥ 1 month?	**0 = NO 1 = YES**

G. Distress or impairment (need 1 for diagnosis)		*Worst Month*
	Sev	*Cx (Sev ≥ 2)?*
(23) Subjective distress		**0 = NO 1 = YES**
(24) Impairment in social functioning		**0 = NO 1 = YES**
(25) Impairment in occupational functioning		**0 = NO 1 = YES**
G subtotals	***G Sev =***	***# G Cx =***

Global ratings		*Worst Month*
(26) Global validity		
(27) Global severity		
(28) Global improvement		

Dissociative symptoms (need 1 for subtype)		*Worst Month*
	Sev	***Sx (Sev ≥ 2)?***
(29) 1 -- Depersonalization		**0 = NO 1 = YES**
(30) 2 – Derealization		**0 = NO 1 = YES**
Dissociative subtotals	***Diss Sev =***	***# Diss Sx =***

PTSD diagnosis		*Worst Month*
PTSD PRESENT – ALL CRITERIA (A-G) MET?		**0 = NO 1 = YES**
With dissociative symptoms		**0 = NO 1 = YES**
(21) With delayed onset (≥ 6 months)		**0 = NO 1 = YES**

APPENDIX E: Cognitive Emotion Regulation Questionnaire (CER-Q)

How do you cope with events?

Everyone gets confronted with negative or unpleasant events now and then and everyone responds to them in his or her own way. By the following questions you are asked to indicate what you generally think, when you experience negative or unpleasant events.

		(almost) never	some-times	regularly	often	(almost) always
1.	I feel that I am the one to blame for it	1	2	3	4	5
2.	I think that I have to accept that this happened	1	2	3	4	5
3.	I often think about how I feel about what I have experienced	1	2	3	4	5
4.	I think of nicer things than what I have experienced	1	2	3	4	5
5.	I think of what I can do best	1	2	3	4	5
6.	I think I can learn something from the situation	1	2	3	4	5
7.	I think that it all could have been much worse	1	2	3	4	5
8.	I often think that what I have experienced is much worse than what others have experienced	1	2	3	4	5
9.	I feel that others are to blame for it	1	2	3	4	5
10.	I feel that I am the one who is responsible for what has happened	1	2	3	4	5
11.	I think that I have to accept the situation	1	2	3	4	5
12.	I am preoccupied with what I think and feel about what I have experienced	1	2	3	4	5
13.	I think of pleasant things that have nothing to do with it	1	2	3	4	5
14.	I think about how I can best cope with the situation	1	2	3	4	5
15.	I think that I can become a stronger person as a result of what has happened	1	2	3	4	5
16.	I think that other people go through much worse experiences	1	2	3	4	5
17.	I keep thinking about how terrible it is what I have experienced	1	2	3	4	5
18.	I feel that others are responsible for what has happened	1	2	3	4	5
19.	I think about the mistakes I have made in this matter	1	2	3	4	5
20.	I think that I cannot change anything about it	1	2	3	4	5
21.	I want to understand why I feel the way I do about what I have experienced	1	2	3	4	5
22.	I think of something nice instead of what has happened	1	2	3	4	5
23.	I think about how to change the situation	1	2	3	4	5
24.	I think that the situation also has its positive sides	1	2	3	4	5

25. I think that it hasn't been too bad compared to other things	1	2	3	4	5
26. I often think that what I have experienced is the worst that can happen to a person	1	2	3	4	5
27. I think about the mistakes others have made in this matter	1	2	3	4	5
28. I think that basically the cause must lie within myself	1	2	3	4	5
29. I think that I must learn to live with it	1	2	3	4	5
30. I dwell upon the feelings the situation has evoked in me	1	2	3	4	5
31. I think about pleasant experiences	1	2	3	4	5
32. I think about a plan of what I can do best	1	2	3	4	5
33. I look for the positive sides to the matter	1	2	3	4	5
34. I tell myself that there are worse things in life	1	2	3	4	5
35. I continually think how horrible the situation has been	1	2	3	4	5
36. I feel that basically the cause lies with others	1	2	3	4	5

APPENDIX F: Life Events Checklist (LEC-5)

Listed below are a number of difficult or stressful things that sometimes happen to people. For each event check one or more of the boxes to the right to indicate that: (a) it *happened to you* personally; (b) you *witnessed it* happen to someone else; (c) you *learned about it* happening to a close family member or close friend; (d) you were exposed to it as *part of your job* (for example, paramedic, police, military, or other first responder); (e) you're *not sure* if it fits; or (f) it *doesn't apply* to you. Be sure to consider your *entire life* (growing up as well as adulthood) as you go through the list of events.

Event	*Happened to me*	*Witnessed it*	*Learned about it*	*Part of my job*	*Not Sure*	*Doesn't Apply*
6. Natural disaster (for example, flood, hurricane, tornado, earthquake)						
2. Fire or explosion						
3. Transportation accident (for example, car accident, boat accident, train wreck, plane crash)						
4. Serious accident at work, home, or during recreational activity						
5. Exposure to toxic substance (for example, dangerous chemicals, radiation)						
6. Physical assault (for example, being attacked, hit, slapped, kicked, beaten up)						
7. Assault with a weapon (for example, being shot, stabbed, threatened with a knife, gun, bomb)						
8. Sexual assault (rape, attempted rape, made to perform any type of sexual act through force or threat of harm)						
9. Other unwanted or uncomfortable sexual experience						
10. Combat or exposure to a war-zone (in the military or as a civilian)						
5. Captivity (for example, being kidnapped, abducted, held hostage, prisoner of war)						
12. Life-threatening illness or injury						
13. Severe human suffering						
14. Sudden violent death (for example, homicide, suicide)						
15. Sudden accidental death						
16. Serious injury, harm, or death you caused to someone else						

17.	**Any other very stressful event or experience**						

APPENDIX G: Mini International Neuropsychiatric Interview

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 5.0.0

DSM-IV

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DISCLAIMER

Our aim is to assist in the assessment and tracking of patients with greater efficiency and accuracy. Before action is taken on any data collected and processed by this program, it should be reviewed and interpreted by a licensed clinician.

This program is not designed or intended to be used in the place of a full medical and psychiatric evaluation by a qualified licensed physician – psychiatrist. It is intended only as a tool to facilitate accurate data collection and processing of symptoms elicited by trained personnel.

M.I.N.I. 5.0.0 (July 1, 2006)

Patient Name:		***Patient Number:***	
Date of Birth:		***Time Interview Began:***	
Interviewer's Name:		***Time Interview Ended:***	
Date of Interview:		***Total Time:***	

	MODULES	TIME FRAME	MEETS CRITERIA	DSM-IV	ICD-10
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks)	†	296.20-296.26 Single	F32.x
		Recurrent	†	296.30-296.36 Recurrent	F33.x
	MDE WITH MELANCHOLIC FEATURES	Current (2 weeks)	†	296.20-296.26 Single	F32.x
	Optional			296.30-296.36 Recurrent	F33.x
B	DYSTHYMIA	Current (Past 2 years)	†	300.4	F34.1
C	SUICIDALITY	Current (Past Month) Risk: † Low † Medium † High	†		
D	MANIC EPISODE	Current	†	296.00-296.06	F30.x-F31.9
		Past	†		
	HYPOMANIC EPISODE	Current	†	296.80-296.89	F31.8-F31.9/F34.0
		Past	†		
E	PANIC DISORDER	Current (Past Month)	†	300.01/300.21	F40.01-F41.0
		Lifetime	†		
F	AGORAPHOBIA	Current	†	300.22	F40.00
G	SOCIAL PHOBIA (Social Anxiety Disorder)	Current (Past Month)	†	300.23	F40.1
H	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	†	300.3	F42.8
I	POSTTRAUMATIC STRESS DISORDER	Current (Past Month)	†	309.81	F43.1
J	ALCOHOL DEPENDENCE	Past 12 Months	†	303.9	F10.2x
	ALCOHOL ABUSE	Past 12 Months	†	305.00	F10.1
K	SUBSTANCE DEPENDENCE (Non-alcohol)	Past 12 Months	†	304.00-.90/305.20-.90	F11.1-F19.1
	SUBSTANCE ABUSE (Non-alcohol)	Past 12 Months	†	304.00-.90/305.20-.90	F11.1-F19.1
L	PSYCHOTIC DISORDERS	Lifetime	†	295.10-295.90/297.1/	F20.xx-F29
		Current	†	297.3/293.81/293.82/ 293.89/298.8/298.9	
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Lifetime	†	296.24/296.34/296.44	F32.3/F33.3/
		Current	†	296.24/296.34/296.44	F30.2/F31.2/F31.5 F31.8/F31.9/F39
M	ANOREXIA NERVOSA	Current (Past 3 Months)	†	307.1	F50.0
N	BULIMIA NERVOSA	Current (Past 3 Months)	†	307.51	F50.2
	ANOREXIA NERVOSA, BINGE EATING/PURGING TYPE	Current	†	307.1	F50.0

O	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	†	300.02	F41.1
P	ANTISOCIAL PERSONALITY DISORDER Optional	Lifetime	†	301.7	F60.2

Which problem troubles you the most? Indicate your response by checking the appropriate check box(es).

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III -R and the CIDI (a structured interview developed by the World Health Organization for lay interviewers for ICD-10) . The results of these studies show that the M.I.N.I. has acceptably high validation and reliability scores, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. It can be used by clinicians, after a brief training session. Lay interviewers require more extensive training.

INTERVIEW:

In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured than usual, with very precise questions about psychological problems which require a yes or no answer.

GENERAL FORMAT:

The M.I.N.I. is divided into **modules** identified by letters, each corresponding to a diagnostic category.

•At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a **gray box**.

•At the end of each module, diagnostic box(es) permit the clinician to indicate whether diagnostic criteria are met.

CONVENTIONS:

Sentences written in « normal font » should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.

Sentences written in « CAPITALS » should not be read to the patient. They are instructions for the interviewer to assist in the scoring of the diagnostic algorithms.

Sentences written in « **bold** » indicate the time frame being investigated. The interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicated should be considered in scoring the responses.

Answers with an arrow above them ( ) indicate that one of the criteria necessary for the diagnosis(es) is not met. In this case, the interviewer should go to the end of the module, circle « **NO** » in all the diagnostic boxes and move to the next module.

When terms are separated by a *slash (/)* the interviewer should read only those symptoms known to be present in the patient (for example, question H6).

Phrases in (parentheses) are clinical examples of the symptom. These may be read to the patient to clarify the question.

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either Yes or No. Clinical judgment by the rater should be used in coding the responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.

The clinician should be sure that <u>each dimension</u> of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives).

<u>Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I.</u> The M.I.N.I. Plus has questions that investigate these issues.

For any questions, suggestions, need for a training session, or information about updates of the M.I.N.I., please contact :

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A. MAJOR DEPRESSIVE EPISODE

(MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

A1	Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks?	NO	YES
A2	In the past two weeks, have you been much less interested in most things or much less able to enjoy the things you used to enjoy most of the time?	NO	YES
	IS **A1** OR **A2** CODED **YES?**	NO	YES

A3 **Over the past two weeks, when you felt depressed or uninterested:**

a	Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (i.e., by ±5% of body weight or ±8 lbs. or ±3.5 kgs., for a 160 lb./70 kg. person in a month)? IF **YES** TO EITHER, CODE **YES.**	NO	YES *
b	Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES
c	Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day?	NO	YES *
d	Did you feel tired or without energy almost every day?	NO	YES
e	Did you feel worthless or guilty almost every day?	NO	YES
f	Did you have difficulty concentrating or making decisions almost every day?	NO	YES
g	Did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead?	NO	YES

ARE **5** OR MORE ANSWERS (**A1-A3**) CODED **YES**?

NO **YES ***

MAJOR DEPRESSIVE EPISODE, CURRENT

IF PATIENT HAS CURRENT MAJOR DEPRESSIVE EPISODE CONTINUE TO A4,
OTHERWISE MOVE TO MODULE B:

A4 a	During your lifetime, did you have other episodes of two weeks or more when you felt depressed or uninterested in most things, and had most of the problems we just talked about?	NO	YES
b	In between 2 episodes of depression, did you ever have an interval of at least 2 months, without any depression and any loss of interest?		

NO **YES**

MAJOR DEPRESSIVE EPISODE, RECURRENT

* If patient has Major Depressive Episode, Current, use this information in coding the corresponding questions on page 5 (A6d, nA6e).

MAJOR DEPRESSIVE EPISODE WITH MELANCHOLIC FEATURES (optional)

(MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

IF THE PATIENT CODES POSITIVE FOR A CURRENT MAJOR DEPRESSIVE EPISODE (**A3** = **YES**), EXPLORE THE FOLLOWING:

A5	a	During the most severe period of the current depressive episode, did you lose almost completely your ability to enjoy nearly everything?	NO	YES
	b	During the most severe period of the current depressive episode, did you lose your ability to respond to things that previously gave you pleasure, or cheered you up? **IF NO:** When something good happens does it fail to make you feel better, even temporarily?	NO	YES
		IS EITHER **A5a** OR **A5b** CODED **YES**?	NO	YES

A6 **Over the past two week period, when you felt depressed and uninterested:**

	a	Did you feel depressed in a way that is different from the kind of feeling you experience when someone close to you dies?	NO	YES
	b	Did you feel regularly worse in the morning, almost every day?	NO	YES
	c	Did you wake up at least 2 hours before the usual time of awakening and have difficulty getting back to sleep, almost every day?	NO	YES
	d	IS **A3c** CODED **YES** (PSYCHOMOTOR RETARDATION OR AGITATION)?	NO	YES
	e	IS **A3a** CODED **YES** FOR ANOREXIA OR WEIGHT LOSS?	NO	YES
	f	Did you feel excessive guilt or guilt out of proportion to the reality of the situation?	NO	YES

ARE **3** OR MORE **A6** ANSWERS CODED **YES**?

NO	**YES**
Major Depressive Episode **with** ***Melancholic Features Current***	

B. DYSTHYMIA

(MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

IF PATIENT'S SYMPTOMS CURRENTLY MEET CRITERIA FOR MAJOR DEPRESSIVE EPISODE, DO NOT EXPLORE THIS MODULE.

B1	Have you felt sad, low or depressed most of the time for the last two years?	NO	YES
B2	Was this period interrupted by your feeling OK for two months or more?	NO	YES
B3	**During this period of feeling depressed most of the time:**		
a	Did your appetite change significantly?	NO	YES
b	Did you have trouble sleeping or sleep excessively?	NO	YES
c	Did you feel tired or without energy?	NO	YES
d	Did you lose your self-confidence?	NO	YES
e	Did you have trouble concentrating or making decisions?	NO	YES
f	Did you feel hopeless?	NO	YES
	ARE **2** OR MORE **B3** ANSWERS CODED **YES**?	NO	YES

B4Did the symptoms of depression cause you significant distress or impair your ability to function at work, socially, or in some other important way?

NO **YES**

DYSTHYMIA
CURRENT

C. SUICIDALITY

In the past month did you:

				Points
C1	Suffer any accident? IF NO TO C1, SKIP TO C2; IF YES, ASK C1a,:	NO	YES	0
C1a	Plan or intend to hurt yourself in that accident either passively or actively? IF NO TO C1a, SKIP TO C2: IF YES, ASK C1b,:	NO	YES	0
C1b	Did you intend to die as a result of this accident?	NO	YES	0
C2	Think that you would be better off dead or wish you were dead?	NO	YES	1
C3	Want to harm yourself or to hurt or to injure yourself?	NO	YES	2
C4	Think about suicide?	NO	YES	6

IF YES, ASK ABOUT THE INTENSITY AND FREQUENCY OF THE SUICIDAL IDEATION:

Frequency	Intensity
Occasionally	Mild
Often	Moderate
Very often	Severe

→ Can you control these impulses and state that you will not act on them while in this program? Only score 8 points if response is NO. NO YES 8

C5	Have a suicide plan?	NO	YES	8
C6	Take any active steps to prepare to injure yourself or to prepare for a suicide attempt in which you expected or intended to die?	NO	YES	9
C7	Deliberately injure yourself without intending to kill yourself?	NO	YES	4
C8	Attempt suicide? Hoped to be rescued / survive Expected / intended to die	NO	YES	10

In your lifetime:

C9	Did you ever make a suicide attempt?	NO	YES	4

IS AT LEAST **1** OF THE ABOVE (EXCEPT C1) CODED **YES**?

NO **YES**

IF YES, ADD THE TOTAL NUMBER OF POINTS FOR THE ANSWERS (C1-C9) CHECKED 'YES' AND SPECIFY THE LEVEL OF SUICIDE RISK AS INDICATED IN THE DIAGNOSTIC BOX:

MAKE ANY ADDITIONAL COMMENTS ABOUT YOUR ASSESSMENT OF THIS PATIENT'S CURRENT AND NEAR FUTURE SUICIDE RISK IN THE SPACE BELOW:

SUICIDE RISK CURRENT

1-8 points	Low
9-16 points	Moderate
≥ 17 points	High

D. (HYPO) MANIC EPISODE

(MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

D1	a Have you **ever** had a period of time when you were feeling 'up' or 'high' or 'hyper' or so full of energy or full of yourself that you got into trouble, or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.) IF PATIENT IS PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN BY 'UP' OR 'HIGH' OR 'HYPER', CLARIFY AS FOLLOWS: By 'up' or 'high' or 'hyper' I mean: having elated mood; increased energy; needing less sleep; having rapid thoughts; being full of ideas; having an increase in productivity, motivation, creativity, or impulsive behavior. IF NO, CODE NO TO **D1b**: IF **YES** ASK:	NO	YES
	b Are you currently feeling 'up' or 'high' or 'hyper' or full of energy?	NO	YES
D2	a Have you **ever** been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified? IF NO, CODE NO TO **D2b**: IF **YES** ASK:	NO	YES
	b Are you currently feeling persistently irritable?	NO	YES
	IS **D1a** OR **D2a** CODED **YES**?	NO	YES

D3 IF **D1b** OR **D2b** = **YES**: EXPLORE THE **CURRENT** AND THE MOST SYMPTOMATIC **PAST** EPISODE, OTHERWISE
IF **D1b** AND **D2b** = **NO**: EXPLORE ONLY THE MOST SYMPTOMATIC **PAST** EPISODE

During the times when you felt high, full of energy, or irritable did you:

		Current Episode		Past Episode	
a	Feel that you could do things others couldn't do, or that you were an especially important person? IF **YES**, ASK FOR EXAMPLES. THE EXAMPLES ARE CONSISTENT WITH A DELUSIONAL IDEA. No Yes	NO	YES	NO	YES
b	Need less sleep (for example, feel rested after only a few hours sleep)?	NO	YES	NO	YES
c	Talk too much without stopping, or so fast that people had difficulty understanding?	NO	YES	NO	YES
d	Have racing thoughts?	NO	YES	NO	YES
e	Become easily distracted so that any little interruption could distract you?	NO	YES	NO	YES
f	Become so active or physically restless that others were worried about you?	NO	YES	NO	YES
g	Want so much to engage in pleasurable activities that you ignored the risks or consequences (for example, spending sprees, reckless driving, or sexual indiscretions)?	NO	YES	NO	YES

	Current Episode		Past Episode	
D3 (SUMMARY): ARE **3** OR MORE **D3** ANSWERS CODED **YES** (OR **4** OR MORE IF **D1a** IS **NO** (IN RATING PAST EPISODE) AND **D1b** IS **NO (**IN RATING CURRENT EPISODE)? RULE: ELATION/EXPANSIVENESS REQUIRES ONLY THREE D3 SYMPTOMS WHILE IRRITABLE MOOD ALONE REQUIRES **4** OF THE **D3** SYMPTOMS. VERIFY IF THE SYMPTOMS OCCURRED DURING THE SAME TIME PERIOD.	NO	YES	NO	YES
D4 Did these symptoms last at least a week **and** cause significant problems at home, at work, socially, or at school, **or** were you hospitalized for these problems?	NO	YES	NO	YES
	↓	↓	↓	↓
THE EPISODE EXPLORED WAS A:	***HYPOMANIC EPISODE***	***MANIC EPISODE***	***HYPOMANIC EPISODE***	***MANIC EPISODE***

IS **D4** CODED **NO**?

SPECIFY IF THE EPISODE IS CURRENT OR PAST.

NO **YES**

HYPOMANIC EPISODE

CURRENT
PAST

IS **D4** CODED **YES**?

SPECIFY IF THE EPISODE IS CURRENT OR PAST.

NO **YES**

MANIC EPISODE

CURRENT
PAST

E. PANIC DISORDER

(MEANS : CIRCLE NO IN E5, E6 AND E7 AND SKIP TO F1)

E1	a	Have you, on more than one occasion, had spells or attacks when you **suddenly** felt anxious, frightened, uncomfortable or uneasy, even in situations where most people would not feel that way?	NO	YES
	b	Did the spells surge to a peak within 10 minutes of starting?	NO	YES
E2		At any time in the past, did any of those spells or attacks come on unexpectedly or occur in an unpredictable or unprovoked manner?	NO	YES
E3		Have you ever had one such attack followed by a month or more of persistent concern about having another attack, or worries about the consequences of the attack or did you make a significant change in your behavior because of the attacks (e.g., shopping only with a companion, not wanting to leave your house, visiting the emergency room repeatedly, or seeing your doctor more frequently because of the symptoms?	NO	YES
E4		**During the worst spell that you can remember:**		
	a	Did you have skipping, racing or pounding of your heart?	NO	YES
	b	Did you have sweating or clammy hands?	NO	YES
	c	Were you trembling or shaking?	NO	YES
	d	Did you have shortness of breath or difficulty breathing?	NO	YES
	e	Did you have a choking sensation or a lump in your throat?	NO	YES
	f	Did you have chest pain, pressure or discomfort?	NO	YES
	g	Did you have nausea, stomach problems or sudden diarrhea?	NO	YES
	h	Did you feel dizzy, unsteady, lightheaded or faint?	NO	YES
	i	Did things around you feel strange, unreal, detached or unfamiliar, or did you feel outside of or detached from part or all of your body?	NO	YES
	j	Did you fear that you were losing control or going crazy?	NO	YES
	k	Did you fear that you were dying?	NO	YES
	l	Did you have tingling or numbness in parts of your body?	NO	YES
	m	Did you have hot flushes or chills?	NO	YES
E5		ARE BOTH **E3,** AND **4** OR MORE **E4** ANSWERS, CODED **YES**?	NO	YES ***PANIC DISORDER LIFETIME***
		IF YES TO E5, SKIP TO E7.		
E6		IF **E5** = **NO,** ARE ANY E4 ANSWERS CODED **YES**?	NO	YES ***LIMITED SYMPTOM ATTACKS LIFETIME***
		THEN SKIP TO **F1.**		

E7	In the past month, did you have such attacks repeatedly (2 or more) followed by persistent concern about having another attack?	NO	YES ***PANIC DISORDER CURRENT***

F. AGORAPHOBIA

F1	Do you feel anxious or uneasy in places or situations where you might have a panic attack or the panic-like symptoms we just spoke about, or where help might not be available or escape might be difficult: like being in a crowd, standing in a line (queue), when you are alone away from home or alone at home, or when crossing a bridge, traveling in a bus, train or car?	NO YES

IF **F1** = **NO**, CIRCLE **NO** IN **F2**.

F2	Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them?	NO YES *AGORAPHOBIA CURRENT*

IS **F2** (CURRENT AGORAPHOBIA) CODED **NO**

and

IS **E7** (CURRENT PANIC DISORDER) CODED **YES**?

NO **YES**

PANIC DISORDER without Agoraphobia CURRENT

IS **F2** (CURRENT AGORAPHOBIA) CODED **YES**

and

IS **E7** (CURRENT PANIC DISORDER) CODED **YES**?

NO **YES**

PANIC DISORDER with Agoraphobia CURRENT

IS **F2** (CURRENT AGORAPHOBIA) CODED **YES**

and

IS **E5** (PANIC DISORDER LIFETIME) CODED **NO**?

NO **YES**

AGORAPHOBIA, CURRENT without history of Panic Disorder

G. SOCIAL PHOBIA (Social Anxiety Disorder)

(MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

G1 In the past month, were you fearful or embarrassed being watched, being NO YES the focus of attention, or fearful of being humiliated? This includes things like speaking in public, eating in public or with others, writing while someone watches, or being in social situations.

G2 Is this social fear excessive or unreasonable? NO YES

G3 Do you fear these social situations so much that you avoid them or suffer through them? NO YES

G4 Do these social fears disrupt your normal work or social functioning or cause you significant distress?

SUBTYPES

Do you fear and avoid 4 or more social situations?

If YES Generalized social phobia (social anxiety disorder)

If NO Non-generalized social phobia (social anxiety disorder)

NOTE TO INTERVIEWER: PLEASE ASSESS WHETHER THE SUBJECT'S FEARS ARE RESTRICTED TO NON-GENERALIZED ("ONLY 1 OR SEVERAL") SOCIAL SITUATIONS OR EXTEND TO GENERALIZED ("MOST") SOCIAL SITUATIONS. "MOST" SOCIAL SITUATIONS IS USUALLY OPERATIONALIZED TO MEAN 4 OR MORE SOCIAL SITUATIONS, ALTHOUGH THE DSM-IV DOES NOT EXPLICITLY STATE THIS.

EXAMPLES OF SUCH SOCIAL SITUATIONSTYPICALLY INCLUDE INITIATING OR MAINTAINING A CONVERSATION, PARTICIPATING IN SMALL GROUPS, DATING, SPEAKING TO AUTHORITY FIGURES, ATTENDING PARTIES, PUBLIC SPEAKING, EATING IN FRONT OF OTHERS, URINATING IN A PUBLIC WASHROOM, ETC.

SOCIAL PHOBIA
(Social Anxiety Disorder)
CURRENT

GENERALIZED

NON-GENERALIZED

H. OBSESSIVE-COMPULSIVE DISORDER

(MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

H1 In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? (For example, the idea that you were dirty, contaminated or had germs, **or** fear of contaminating others, **or** fear of harming someone even though you didn't want to, **or** fearing you would act on some impulse, **or** fear or superstitions that you would be responsible for things going wrong, **or** obsessions with sexual thoughts, images or impulses, **or** hoarding, collecting, **or** religious obsessions.)

(DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS. DO NOT INCLUDE OBSESSIONS DIRECTLY RELATED TO EATING DISORDERS, SEXUAL DEVIATIONS, PATHOLOGICAL GAMBLING, OR ALCOHOL OR DRUG ABUSE BECAUSE THE PATIENT MAY DERIVE PLEASURE FROM THE ACTIVITY AND MAY WANT TO RESIST IT ONLY BECAUSE OF ITS NEGATIVE CONSEQUENCES.)

NO YES
↓
SKIP TO **H4**

H2 Did they keep coming back into your mind even when you tried to ignore or get rid of them?

NO YES
↓
SKIP TO **H4**

H3 Do you think that these obsessions are the product of your own mind and that they are not imposed from the outside?

NO YES
obsessions

H4 In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively, counting or checking things over and over, or repeating, collecting, arranging things, or other superstitious rituals?

NO YES
compulsions

IS **H3** OR **H4** CODED **YES**?

NO YES

H5 Did you recognize that either these obsessive thoughts or these compulsive behaviors were excessive or unreasonable?

NO YES

H6 Did these obsessive thoughts and/or compulsive behaviors significantly interfere with your normal routine, your work or school, your usual social activities, or relationships, or did they take more than one hour a day?

NO **YES**

O.C.D. CURRENT

J. ALCOHOL ABUSE AND DEPENDENCE

(MEANS: GO TO DIAGNOSTIC BOXES, CIRCLE NO IN BOTH AND MOVE TO THE NEXT MODULE)

J1	**In the past 12 months**, have you had 3 or more alcoholic drinks within a 3 hour period on 3 or more occasions?	NO	YES

J2 **In the past 12 months**:

a	Did you need to drink more in order to get the same effect that you got when you first started drinking?	NO	YES
b	When you cut down on drinking did your hands shake, did you sweat or feel agitated? Did you drink to avoid these symptoms or to avoid being hungover, for example, "the shakes", sweating or agitation? IF **YES** TO EITHER, CODE **YES**.	NO	YES
7.	During the times when you drank alcohol, did you end up drinking more than you planned when you started?	NO	YES
8.	Have you tried to reduce or stop drinking alcohol but failed?	NO	YES
9.	On the days that you drank, did you spend substantial time in obtaining alcohol, drinking, or in recovering from the effects of alcohol?	NO	YES
10.	Did you spend less time working, enjoying hobbies, or being with others because of your drinking?	NO	YES
11.	Have you continued to drink even though you knew that the drinking caused you health or mental problems?	NO	YES

ARE **3** OR MORE **J2** ANSWERS CODED **YES**?

***** IF YES, SKIP J3 QUESTIONS, CIRCLE N/A IN THE ABUSE BOX AND MOVE TO THE NEXT DISORDER. DEPENDENCE PREEMPTS ABUSE.

NO **YES***

ALCOHOL DEPENDENCE
CURRENT

J3 **In the past 12 months:**

a	Have you been intoxicated, high, or hungover more than once when you had other responsibilities at school, at work, or at home? Did this cause any problems? (CODE **YES** ONLY IF THIS CAUSED PROBLEMS.)	NO	YES
b	Were you intoxicated more than once in any situation where you were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?	NO	YES
c	Did you have legal problems more than once because of your drinking, for example, an arrest or disorderly conduct?	NO	YES
d	Did you continue to drink even though your drinking caused problems with your family or other people?	NO	YES

NO

ARE **1** OR MORE **J3** ANSWERS CODED **YES**?

N/A **YES**

K. NON-ALCOHOL PSYCHOACTIVE SUBSTANCE USE DISORDERS

(MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

Now I am going to show you / read to you a list of street drugs or medicines.

K1 a **In the past 12 months**, did you take any of these drugs more than once, to get high, to feel better, or to change your mood? NO YES

CIRCLE EACH DRUG TAKEN:

Stimulants: amphetamines, "speed", crystal meth, "crank", "rush", Dexedrine, Ritalin, diet pills.

Cocaine: snorting, IV, freebase, crack, "speedball".

Narcotics: heroin, morphine, Dilaudid, opium, Demerol, methadone, codeine, Percodan, Darvon, OxyContin.

Hallucinogens: LSD ("acid"), mescaline, peyote, PCP ("angel dust", "peace pill"), psilocybin, STP, "mushrooms", "ecstasy", MDA, MDMA, or ketamine ("special K").

Inhalants: "glue", ethyl chloride, "rush", nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers").

Marijuana: hashish ("hash"), THC, "pot", "grass", "weed", "reefer".

Tranquilizers: Quaalude, Seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown, GHB, Roofinol, "Roofies".

Miscellaneous: steroids, nonprescription sleep or diet pills. Any others?

SPECIFY MOST USED DRUG(S): _____

CHECK ONE BOX

ONLY ONE DRUG / DRUG CLASS HAS BEEN USED ☐

ONLY THE MOST USED DRUG CLASS IS INVESTIGATED. | |

EACH DRUG CLASS USED IS EXAMINED SEPARATELY (PHOTOCOPY K2 AND K3 AS NEEDED)

5. SPECIFY WHICH DRUG/DRUG CLASS WILL BE EXPLORED IN THE INTERVIEW BELOW IF THERE IS CONCURRENT OR SEQUENTIAL POLYSUBSTANCE USE:_____

K2 **Considering your use of (NAME THE DRUG / DRUG CLASS SELECTED), in the past 12 months:**

a Have you found that you needed to use more (NAME OF DRUG / DRUG CLASS SELECTED) to get the same effect that you did when you first started taking it? NO YES

b When you reduced or stopped using (NAME OF DRUG / DRUG CLASS SELECTED), did you have withdrawal symptoms (aches, shaking, fever, weakness, diarrhea, nausea, sweating, heart pounding, difficulty sleeping, or feeling agitated, anxious, irritable, or depressed)? Did you use any drug(s) to keep yourself from getting sick (withdrawal symptoms) or so that you would feel better? NO YES

IF **YES** TO EITHER, CODE **YES**.

c Have you often found that when you used (NAME OF DRUG / DRUG CLASS SELECTED), you ended up taking more than you thought you would? NO YES

d Have you tried to reduce or stop taking (NAME OF DRUG / DRUG CLASS SELECTED) but failed? NO YES

e On the days that you used (NAME OF DRUG / DRUG CLASS SELECTED), did you spend substantial time (>2 HOURS), obtaining, using or in recovering from the drug, or thinking about the drug? NO YES

f Did you spend less time working, enjoying hobbies, or being with family or friends because of your drug use? NO YES

g Have you continued to use (NAME OF DRUG / DRUG CLASS SELECTED), even though it caused you health or mental problems? NO YES

ARE **3** OR MORE **K2** ANSWERS CODED **YES**? **NO YES ***

SPECIFY DRUG(S): _____

SUBSTANCE DEPENDENCE
CURRENT

***** IF YES, SKIP K3 QUESTIONS, CIRCLE N/A IN THE ABUSE BOX FOR THIS SUBSTANCE AND MOVE TO THE NEXT DISORDER. DEPENDENCE PREEMPTS ABUSE.

Considering your use of (NAME THE DRUG CLASS SELECTED), in the past 12 months:

K3 a Have you been intoxicated, high, or hungover from (NAME OF DRUG / DRUG CLASS SELECTED) more than once, when you had other responsibilities at school, at work, or at home? Did this cause any problem? NO YES

(CODE **YES** ONLY IF THIS CAUSED PROBLEMS.)

b Have you been high or intoxicated from (NAME OF DRUG / DRUG CLASS SELECTED) more than once in any situation where you were physically at risk (for example, driving a car, riding a motorbike, using machinery, boating, etc.)? NO YES

7. Did you have legal problems more than once because of your drug use, for example, an arrest or disorderly conduct? NO YES

8. Did you continue to use (NAME OF DRUG / DRUG CLASS SELECTED), even though it caused problems with your family or other people? NO YES

ARE **1** OR MORE **K3** ANSWERS CODED **YES**? **NO N/A YES**

SPECIFY DRUG(S): _____

SUBSTANCE ABUSE
CURRENT

L. PSYCHOTIC DISORDERS AND MOOD DISORDER WITH PSYCHOTIC FEATURES

ASK FOR AN EXAMPLE OF EACH QUESTION ANSWERED POSITIVELY. CODE **YES** ONLY IF THE EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHT OR OF PERCEPTION OR IF THEY ARE NOT CULTURALLY APPROPRIATE. BEFORE CODING, INVESTIGATE WHETHER DELUSIONS QUALIFY AS "BIZARRE". DELUSIONS ARE "BIZARRE" IF: CLEARLY IMPLAUSIBLE, ABSURD, NOT UNDERSTANDABLE, AND CANNOT DERIVE FROM ORDINARY LIFE EXPERIENCE. HALLUCINATIONS ARE SCORED "BIZARRE" IF: A VOICE COMMENTS ON THE PERSON'S THOUGHTS OR BEHAVIOR, OR WHEN TWO OR MORE VOICES ARE CONVERSING WITH EACH OTHER.

					BIZARRE
	Now I am going to ask you about unusual experiences that some people have.				
L1	a Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you? **NOTE**: ASK FOR EXAMPLES TO RULE OUT ACTUAL STALKING.	NO	YES		YES
	b **IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES		YES **L6**
L2	a Have you ever believed that someone was reading your mind or could hear your thoughts, or that you could actually read someone's mind or hear what another person was thinking?	NO	YES		YES
	b **IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES		YES **L6**
L3	a Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? CLINICIAN: ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC.	NO	YES		YES
	b **IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES		YES **L6**
L4	a Have you ever believed that you were being sent special messages through the TV, radio, or newspaper, or that a person you did not personally know was particularly interested in you?	NO	YES		YES
	b **IF YES OR YES BIZARRE:** do you currently believe these things?	NO	YES		YES **L6**
L5	a Have your relatives or friends ever considered any of your beliefs strange or unusual? INTERVIEWER: ASK FOR EXAMPLES. ONLY CODE **YES** IF THE EXAMPLES ARE **CLEARLY** DELUSIONAL IDEAS NOT EXPLORED IN QUESTIONS L1 TO L4, FOR EXAMPLE, SOMATIC OR RELIGIOUS DELUSIONS OR DELUSIONS OF GRANDIOSITY, JEALOUSY, GUILT, RUIN OR DESTITIUTION, ETC.	NO	YES		YES
	b **IF YES OR YES BIZARRE:** do they currently consider your beliefs strange?	NO	YES		YES
L6	a Have you ever heard things other people couldn't hear, such as voices? HALLUCINATIONS ARE SCORED "BIZARRE" ONLY IF PATIENT ANSWERS **YES** TO THE FOLLOWING:	NO	YES		
	IF YES: Did you hear a voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO			YES
	b **IF YES OR YES BIZARRE TO L6a:** have you heard these things in the past month? HALLUCINATIONS ARE SCORED "BIZARRE" ONLY IF PATIENT ANSWERS **YES** TO THE FOLLOWING: Did you hear a voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?	NO	YES		YES **L8b**

L7 a Have you ever had visions when you were awake or have you ever seen things other people couldn't see? NO YES

CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.

b **IF YES:** have you seen these things in the past month? NO YES

CLINICIAN'S JUDGMENT

L8 b IS THE PATIENT CURRENTLY EXHIBITING INCOHERENCE, DISORGANIZED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS? NO YES

L9 b IS THE PATIENT CURRENTLY EXHIBITING DISORGANIZED OR CATATONIC BEHAVIOR? NO YES

L10 b ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, E.G. SIGNIFICANT AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION), PROMINENT DURING THE INTERVIEW? NO YES

L11 a ARE 1 OR MORE « a » QUESTIONS FROM L1a TO L7a CODED **YES OR YES BIZARRE** AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT OR RECURRENT)
OR
MANIC OR HYPOMANIC EPISODE, (CURRENT OR PAST) CODED **YES**? NO YES

L13

IF NO TO L11 a, CIRCLE NO IN BOTH 'MOOD DISORDER WITH PSYCHOTIC FEATURES' DIAGNOSTIC BOXES AND MOVE TO L13.

b You told me earlier that you had period(s) when you felt (depressed/high/persistently irritable). **NO** **YES**

Were the beliefs and experiences you just described (SYMPTOMS CODED **YES** FROM **L1**a TO **L7**a) restricted exclusively to times when you were feeling depressed/high/irritable?

MOOD DISORDER WITH
PSYCHOTIC FEATURES

IF THE PATIENT EVER HAD A PERIOD OF AT LEAST 2 WEEKS OF HAVING THESE BELIEFS OR EXPERIENCES (PSYCHOTIC SYMPTOMS) WHEN THEY WERE NOT DEPRESSED/HIGH/IRRITABLE, CODE NO TO THIS DISORDER.

LIFETIME

IF THE ANSWER IS NO TO THIS DISORDER, ALSO CIRCLE NO TO L12 AND MOVE TO L13

L12 a ARE 1 OR MORE « b » QUESTIONS FROM L1b TO L7b CODED **YES OR YES BIZARRE** AND IS EITHER: **NO** **YES**

MAJOR DEPRESSIVE EPISODE, (CURRENT)
OR
MANIC OR HYPOMANIC EPISODE, (CURRENT) CODED **YES**?

MOOD DISORDER WITH
PSYCHOTIC FEATURES

IF THE ANSWER IS YES TO THIS DISORDER (LIFETIME OR CURRENT), CIRCLE NO TO L13 AND L14 AND MOVE TO THE NEXT MODULE.

CURRENT

L13 ARE 1 OR MORE « b » QUESTIONS FROM L1b TO L6b, CODED **YES BIZARRE**? **NO** **YES**

OR

ARE 2 OR MORE « b » QUESTIONS FROM L1b TO L10b, CODED **YES** (RATHER THAN **YES BIZARRE**)?

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1 MONTH PERIOD?

PSYCHOTIC DISORDER
CURRENT

L14 IS **L13** CODED **YES** **NO** **YES**

OR

ARE 1 OR MORE « a » QUESTIONS FROM L1a TO L6a, CODED **YES BIZARRE**?

OR

ARE 2 OR MORE « a » QUESTIONS FROM L1a TO L7a, CODED **YES** (RATHER THAN **YES BIZARRE**)

AND DID AT LEAST TWO OF THE PSYCHOTIC SYMPTOMS OCCUR DURING THE SAME 1 MONTH PERIOD?

PSYCHOTIC DISORDER
LIFETIME

M. ANOREXIA NERVOSA

(MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

M1 a How tall are you? ft in.

cm.

b. What was your lowest weight in the past 3 months? lbs.

kgs.

c IS PATIENT'S WEIGHT EQUAL TO OR BELOW THE THRESHOLD CORRESPONDING TO HIS / HER HEIGHT? (SEE TABLE BELOW) NO YES

In the past 3 months:

M2 In spite of this low weight, have you tried not to gain weight? NO YES

M3 Have you intensely feared gaining weight or becoming fat, even though you were underweight? NO YES

M4 a Have you considered yourself too big / fat or that part of your body was too big / fat? NO YES

b Has your body weight or shape greatly influenced how you felt about yourself? NO YES

c Have you thought that your current low body weight was normal or excessive? NO YES

M5 ARE 1 OR MORE ITEMS FROM **M4** CODED **YES**? NO YES

M6 FOR WOMEN ONLY: During the last 3 months, did you miss all your menstrual periods when they were expected to occur (when you were not pregnant)? NO YES

FOR WOMEN:ARE **M5 AND M6** CODED **YES**?

FOR MEN: IS **M5** CODED **YES**?

NO YES

***ANOREXIA NERVOSA* CURRENT**

HEIGHT / WEIGHT TABLE CORRESPONDING TO A BMI THRESHOLD OF 17.5 KG/M^2

Height/Weight														
ft/in	4'9	4'10	4'11	5'0	5'1	5'2	5'3	5'4	5'5	5'6	5'7	5'8	5'9	5'10
lbs.	81	84	87	89	92	96	99	102	105	108	112	115	118	122
cm	145	147	150	152	155	158	160	163	165	168	170	173	175	178
kgs	37	38	39	41	42	43	45	46	48	49	51	52	54	55

Height/Weight					
ft/in	5'11	6'0	6'1	6'2	6'3
lbs.	125	129	132	136	140
cm	180	183	185	188	191
kgs	57	59	60	62	64

The weight thresholds above are calculated using a body mass index (BMI) equal to or below 17.5 kg/m^2 for the patient's height. This is the threshold guideline below which a person is deemed underweight by the DSM-IV and the ICD-10 Diagnostic Criteria for Research for Anorexia Nervosa.

N. BULIMIA NERVOSA

(MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

N1	In the past three months, did you have eating binges or times when you ate a very large amount of food within a 2-hour period?	NO	YES
N2	In the last 3 months, did you have eating binges as often as twice a week?	NO	YES
N3	During these binges, did you feel that your eating was out of control?	NO	YES
N4	Did you do anything to compensate for, or to prevent a weight gain from these binges, like vomiting, fasting, exercising or taking laxatives, enemas, diuretics (fluid pills), or other medications?	NO	YES
N5	Does your body weight or shape greatly influence how you feel about yourself?	NO	YES
N6	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?	NO	YES ↓ Skip to N8
N7	Do these binges occur only when you are under (____lbs./kgs.)? INTERVIEWER: WRITE IN THE ABOVE PARENTHESIS THE THRESHOLD WEIGHT FOR THIS PATIENT'S HEIGHT FROM THE HEIGHT / WEIGHT TABLE IN THE ANOREXIA NERVOSA MODULE.	NO	YES

N8 IS **N5** CODED **YES** AND IS EITHER **N6** OR **N7** CODED **NO**?

NO **YES**

BULIMIA NERVOSA
CURRENT

IS **N7** CODED **YES**?

NO **YES**

ANOREXIA NERVOSA
Binge Eating/Purging Type
CURRENT

O. GENERALIZED ANXIETY DISORDER

(MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

O1	a	Have you worried excessively or been anxious about several things over the past 6 months?	NO	YES
	b	Are these worries present most days?	NO	YES
		IS THE PATIENT'S ANXIETY RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY, ANY DISORDER PRIOR TO THIS POINT?	NO	YES
O2		Do you find it difficult to control the worries or do they interfere with your ability to focus on what you are doing?	NO	YES
O3		FOR THE FOLLOWING, CODE **NO** IF THE SYMPTOMS ARE CONFINED TO FEATURES OF ANY DISORDER EXPLORED PRIOR TO THIS POINT**.**		
		When you were anxious over the past 6 months, did you, most of the time:		
	a	Feel restless, keyed up or on edge?	NO	YES
	b	Feel tense?	NO	YES
	c	Feel tired, weak or exhausted easily?	NO	YES
	d	Have difficulty concentrating or find your mind going blank?	NO	YES
	e	Feel irritable?	NO	YES
	f	Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES

ARE **3** OR MORE **O3** ANSWERS CODED **YES**?

NO **YES**

GENERALIZED ANXIETY DISORDER
CURRENT

P. ANTISOCIAL PERSONALITY DISORDER (optional)

(MEANS : GO TO THE DIAGNOSTIC BOX AND CIRCLE NO.)

P1 **Before you were 15 years old, did you:**

a	repeatedly skip school or run away from home overnight?	NO	YES
b	repeatedly lie, cheat, "con" others, or steal?	NO	YES
c	start fights or bully, threaten, or intimidate others?	NO	YES
d	deliberately destroy things or start fires?	NO	YES
e	deliberately hurt animals or people?	NO	YES
f	force someone to have sex with you?	NO	YES
	ARE **2** OR MORE **P1** ANSWERS CODED **YES**?	NO	YES

DO NOT CODE **YES** TO THE BEHAVIORS BELOW IF THEY ARE EXCLUSIVELY POLITICALLY OR RELIGIOUSLY MOTIVATED**.**

P2 **Since you were 15 years old, have you:**

a	repeatedly behaved in a way that others would consider irresponsible, like failing to pay for things you owed, deliberately being impulsive or deliberately not working to support yourself?	NO	YES
b	done things that are illegal even if you didn't get caught (for example, destroying property, shoplifting, stealing, selling drugs, or committing a felony)?	NO	YES
c	been in physical fights repeatedly (including physical fights with your spouse or children)?	NO	YES
d	often lied or "conned" other people to get money or pleasure, or lied just for fun?	NO	YES
e	exposed others to danger without caring?	NO	YES
f	felt no guilt after hurting, mistreating, lying to, or stealing from others, or after damaging property?	NO	YES

ARE **3** OR MORE **P2** QUESTIONS CODED **YES**?

NO	**YES**
ANTISOCIAL PERSONALITY DISORDER **LIFETIME**	

THIS CONCLUDES THE INTERVIEW

REFERENCES

Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Janavs J, Weiller E, Bonara LI, Keskiner A, Schinka J, Knapp E, Sheehan MF, Dunbar GC. Reliability and Validity of the MINI International Neuropsychiatric Interview (M.I.N.I.): According to the SCID-P. European Psychiatry. 1997; 12:232-241.

Lecrubier Y, Sheehan D, Weiller E, Amorim P, Bonora I, Sheehan K, Janavs J, Dunbar G. The MINI International Neuropsychiatric Interview (M.I.N.I.) A Short Diagnostic Structured Interview: Reliability and Validity According to the CIDI. European Psychiatry. 1997; 12: 224-231.

Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar G: The Mini International Neuropsychiatric Interview (M.I.N.I.): The Development and Validation of a Structured Diagnostic Psychiatric Interview. J. Clin Psychiatry, 1998;59(suppl 20):22-33.

Amorim P, Lecrubier Y, Weiller E, Hergueta T, Sheehan D: DSM-III-R Psychotic Disorders: procedural validity of the Mini International Neuropsychiatric Interview (M.I.N.I.). Concordance and causes for discordance with the CIDI. European Psychiatry. 1998; 13:26-34.

Translations	**M.I.N.I. 4.4 or earlier versions**	**M.I.N.I. 4.6/5.0, M.I.N.I. Plus 4.6/5.0 and M.I.N.I. Screen 5.0:**
Afrikaans	R. Emsley	W. Maartens
Arabic		O. Osman, E. Al-Radi
Bengali		H. Banerjee, A. Banerjee
Braille (English)		
Brazilian Portuguese	P. Amorim	P. Amorim
Bulgarian	L.G.. Hranov	
Chinese		L. Carroll, Y-J. Lee, Y-S. Chen, C-C. Chen, C-Y. Liu, C-K. Wu, H-S. Tang, K-D. Juang, Yan-Ping Zheng.
Czech		P. Zvlosky
Danish	P. Bech	P. Bech, T. Schütze
Dutch/Flemish	E. Griez, K. Shruers, T. Overbeek, K. Demyttenaere	I. Van Vliet, H. Leroy, H. van Megen
English	D. Sheehan, J. Janavs, R. Baker, K. Harnett-Sheehan, E. Knapp, M. Sheehan	D. Sheehan, R. Baker, J. Janavs, K. Harnett-Sheehan, M. Sheehan
Estonian		J. Shlik, A. Aluoja, E. Khil
Farsi/Persian		K. Khooshabi, A. Zomorodi
Finnish	M. Heikkinen, M. Lijeström, O. Tuominen	M. Heikkinen, M. Lijeström, O. Tuominen
French	Y. Lecrubier, E. Weiller, I. Bonora, P. Amorim, J.P. Lepine	Y. Lecrubier, E. Weiller, P. Amorim, T. Hergueta
German	I. v. Denffer, M. Ackenheil, R. Dietz-Bauer	G. Stotz, R. Dietz-Bauer, M. Ackenheil
Greek	S. Beratis	T. Calligas, S. Beratis
Gujarati		M. Patel, B. Patel, Organon
Hebrew	J. Zohar, Y. Sasson	R. Barda, I. Levinson, A. Aviv
Hindi		C. Mittal, K. Batra, S. Gambhir, Organon
Hungarian	I. Bitter, J. Balazs	I. Bitter, J. Balazs
Icelandic		J.G. Stefansson
Italian	I. Bonora, L. Conti, M. Piccinelli, M. Tansella, G. Cassano, Y. Lecrubier, P. Donda, E. Weiller	L. Conti, A. Rossi, P. Donda
Japanese		T. Otsubo, H. Watanabe, H. Miyaoka, K. Kamijima, J.Shinoda, K.Tanaka, Y. Okajima
Kannada		Organon
Korean		K.S. Oh and Korean Academy of Anxiety Disorders
Latvian	V. Janavs, J. Janavs, I. Nagobads	V. Janavs, J. Janavs
Lithuanian		A. Bacevicius
Malayalam		Organon
Marathi		Organon
Norwegian	G. Pedersen, S. Blomhoff	K.A. Leiknes , U. Malt, E. Malt, S. Leganger
Polish	M. Masiak, E. Jasiak	M. Masiak, E. Jasiak
Portuguese	P. Amorim	P. Amorim, T. Guterres
Punjabi		A. Gahunia, S. Gambhir
Romanian		O. Driga
Russian		A. Bystritsky, E. Selivra, M. Bystritsky, L. Shumyak, M. Klisinska.
Serbian	I. Timotijevic	I. Timotijevic
Setswana		K. Ketlogetswe
Slovenian		M. Kocmur, M. Kocmur
Spanish	L. Ferrando, J. Bobes-Garcia, J. Gilbert-Rahola, Y. Lecrubier	L. Ferrando, L. Franco-Alfonso, M. Soto, J. Bobes-Garcia, O. Soto, L. Franco, G. Heinze, C. Santana, R. Hidalgo
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Tamil		Organon
Telugu		Organon

Thai		P. Kittirattanapaiboon, S. Mahatnirunkul, P. Udomrat, P. Silpakit,, M. Khamwongpin, S. Srikosai.
Turkish	T. Örnek, A. Keskiner, I. Vahip	T. Örnek, A. Keskiner, A.Engeler
Urdu		S. Gambhir

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APPENDIX H: Previous Head Trauma Questionnaire

The next few questions are about previous head trauma you may have experienced.

Have you ever sustained a head injury (concussion, traumatic brain injury) in the past? **Yes** ____ **No** ____

If **no**, move to the State-Trait Anxiety Inventory.

If **yes**, when did you sustain this injury (estimated month/year) ?
_____

Did you lose consciousness following this injury? **Yes** ____ **No** ____

If yes, for how long? _____

Check off any of the following symptoms that you experienced following this injury.

- ☐ Seizures
- ☐ Behavioral changes
- ☐ Mood changes
- ☐ Headaches
- ☐ Difficulty speaking
- ☐ Fatigue
- ☐ Insomnia
- ☐ Changes in sleep patterns
- ☐ Loss of bladder control
- ☐ Blindness
- ☐ Dilated or unequal pupils
- ☐ Hearing changes
- ☐ Weakness / Poor coordination
- ☐ Paralysis / Difficulty moving body parts
- ☐ Numbness and tingling
- ☐ Irritability / Depression / Anxiety
- ☐ Confusion / Memory Problems / Difficulty Thinking
- ☐ Loss in Problem Solving Abilities
- ☐ Nausea
- ☐ Bad taste in the mouth
- ☐ Sensitivity to light or noise
- ☐ Loss of eye movement
- ☐ Blurred Vision
- ☐ Ringing in the ears

How long did you experience these symptoms after your injury? _____

APPENDIX I: Rumination Questionnaire (RQ)

ID #: _____ Date: _____ Interviewer: _____

RQ

People think and do many different things when they feel sad, blue, or depressed. Below is a list of possibilities about how people might respond. Please read these items and indicate whether you never, sometimes, often, or always think or do each one when you feel down, sad, or depressed. Please indicate what you generally do, not what you think you should do.

1 = almost never 2 = sometimes 3 = often 4 = almost always

1.) Analyze recent events to try to understand why you are depressed ___

2.) Go away by yourself and think about why you feel this way ___

3.) Write down what you are thinking and analyze it ___

4.) Analyze your personality to try to understand why you are depressed ___

5.) Go someplace alone to think about your feelings ___

6.) Think "What am I doing to deserve this?" ___

7.) Think "Why do I always react this way?" ___

8.) Think about a recent situation, wishing it had gone better ___

9.) Think "Why do I have problems other people don't have?" ___

10.) Think "Why can't I handle things better?" ___

APPENDIX J: State-Trait Anxiety Questionnaire

State-Trait Anxiety Inventory FORM Y-1

Developed by C.D.Spielberger, R.L. Gorsuch and R.Lushene

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of statement to indicate how you *feel* **right now**, that is, ***at this moment***. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	NOT AT ALL	SOMEWHAT	MODERATELLY	VERY MUCH
1. I feel calm	①	②	③	④
2. I feel secure	①	②	③	④
3. I am tense	①	②	③	④
4. I feel strained	①	②	③	④
5. I feel at ease	①	②	③	④
6. I feel upset	①	②	③	④
7. I am presently worrying over possible misfortunes	①	②	③	④
8. I feel satisfied	①	②	③	④
9. I feel frightened	①	②	③	④
10. I feel comfortable	①	②	③	④
11. I feel self-confident	①	②	③	④
12. I feel nervous	①	②	③	④
13. I am jittery	①	②	③	④
14. I feel indecisive	①	②	③	④
15. I am relaxed	①	②	③	④
16. I feel content	①	②	③	④
17. I am worried	①	②	③	④
18. I feel confused	①	②	③	④
19. I feel steady	①	②	③	④
20. I feel pleasant	①	②	③	④

State-Trait Anxiety Inventory FORM Y-2

Developed by C.D.Spielberger, R.L. Gorsuch and R.Lushene

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of statement to indicate how you **generally** *feel*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	NOT AT ALL	SOMEWHAT	MODERATELLY	VERY MUCH
21. I feel pleasant	①	②	③	④
22. I feel nervous and restless	①	②	③	④
23. I feel satisfied with myself	①	②	③	④
24. I wish I could be as happy as others seem to be	①	②	③	④
25. I feel like a failure	①	②	③	④
26. I feel rested	①	②	③	④
27. I am "calm, cool and collected"	①	②	③	④
28. I feel that difficulties are piling up so that I cannot overcome them	①	②	③	④
29. I worry too much over something that really doesn't matter	①	②	③	④
30. I am happy	①	②	③	④
31. I have disturbing thoughts	①	②	③	④
32. I lack self-confidence	①	②	③	④
33. I feel secure	①	②	③	④
34. I make decisions easily	①	②	③	④
35. I feel inadequate	①	②	③	④
36. I am content	①	②	③	④
37. Some unimportant thought runs through my mind and bothers me	①	②	③	④
38. I take disappointments so keenly that I can't put them out of my mind	①	②	③	④
39. I am a steady person	①	②	③	④
40. I get in a state of tension or turmoil as I think over my recent concerns and interests	①	②	③	④

REFERENCES

Adler, L. a, Kunz, M., Chua, H. C., Rotrosen, J., & Resnick, S. G. (2004). Attention-deficit/hyperactivity disorder in adult patients with posttraumatic stress disorder (PTSD): is ADHD a vulnerability factor? *J Atten.Disord*, *8*(1087–547), 11–16. http://doi.org/10.1177/108705470400800102

Adólfsdóttir, S., Sørensen, L., & Lundervold, A. J. (2008). The attention network test: a characteristic pattern of deficits in children with ADHD. *Behavioral and Brain Functions : BBF*, *4*, 9. http://doi.org/10.1186/1744-9081-4-9

Alliance., P. (2001). Posttraumatic stress disorder: a guide for the Frontline August 2000, PTSD alliance.

Amado-Boccara, I., Gougoulis, N., Poirier Littré, M. F., Galinowski, A., & Lôo, H. (1995). Effects of antidepressants on cognitive functions: A review. *Neuroscience and Biobehavioral Reviews*, *19*(3), 479–493. http://doi.org/10.1016/0149-7634(94)00068-C

American Psychiatric Association. (2013). *DSM-V. American Journal of Psychiatry*. http://doi.org/10.1176/appi.books.9780890425596.744053

Amstadter, A. B. (2008). Emotion regulation and anxiety disorders. *Journal of Anxiety Disorders*, *22*(2), 211–221. http://doi.org/10.1016/j.janxdis.2007.02.004

Anderson, J. S., Druzgal, T. J., Lopez-Larson, M., Jeong, E.-K., Desai, K., & Yurgelun-Todd, D. (2011). Network anticorrelations, global regression, and phase-shifted soft tissue correction. *Human Brain Mapping*, *32*(6), 919–34. http://doi.org/10.1002/hbm.21079

Anticevic, A., Cole, M. W., Murray, J. D., Corlett, P. R., Wang, X.-J., & Krystal, J. H. (2012). The role of default network deactivation in cognition and disease. *Trends in Cognitive Sciences*, *16*(12), 584–592. http://doi.org/10.1016/j.tics.2012.10.008

Armengol, C. G., & Cavanaugh-Sawan, A. (2003). Differential Performance of Post-traumatic stress disorder (PTSD), Attention deficit hyperactivity disorder (ADHD), and a Non-Clinical Control Group on Tests of Attention and Inhibition. *Revista Española de Neuropsicología*, *5*(1), 65–79.

Aupperle, R. L., Melrose, A. J., Stein, M. B., & Paulus, M. P. (2012). Executive function and PTSD: Disengaging from trauma. *Neuropharmacology*, *62*(2), 686–694. http://doi.org/10.1016/j.neuropharm.2011.02.008

Aupperle, R. L., Stillman, A. N., Simmons, A. N., Flagan, T., Allard, C. B., Thorp, S. R., … Stein, M. B. (2016). Intimate Partner Violence PTSD and Neural Correlates of Inhibition. *Journal of Traumatic Stress*, *29*(1), 33–40. http://doi.org/10.1002/jts.22068

Awh, E., Vogel, E. K., & Oh, S.-H. (2006). Interactions between attention and working memory. *Neuroscience*, *139*(1), 201–208. http://doi.org/10.1016/j.neuroscience.2005.08.023

Bardeen, J. R., Tull, M. T., Daniel, T. A., Evenden, J., & Stevens, E. N. (2016). A Preliminary Investigation of the Time Course of Attention Bias Variability in Posttraumatic Stress Disorder: The Moderating Role of Attentional Control. *Behaviour Change*, *33*(2), 94–111. http://doi.org/10.1017/bec.2016.5

Barlow-Ogden, K., & Poynter, W. (2012). Mild traumatic brain injury and posttraumatic stress disorder: investigation of visual attention in Operation Iraqi Freedom/Operation Enduring Freedom veterans. *Journal of Rehabilitation Research and Development*, *49*(7), 1101–14. http://doi.org/10.1682/JRRD.2010.09.0188

Barrett, L. F., & Satpute, A. B. (2013). Large-scale brain networks in affective and social neuroscience: Towards an integrative functional architecture of the brain. *Current Opinion in Neurobiology*. http://doi.org/10.1016/j.conb.2012.12.012

Bennett, T., Raymond, M., Malia, K., Bewick, K., & Linton, B. (1998). Rehabilitation of attention and concentration deficits following brain injury. *Journal of Cognitive Rehabilitation*, 8–13.

Beran, M., Washburn, D., & Kleinman, S. (2003). Attention Network Task (ANT) performance by children and rhesus monkeys. In *44th Annual Meeting of the Psychonomic Society, Vancouver, Canada*.

Berg, E. A. (1948). A simple objective technique for measuring flexibility in thinking. *The Journal of General Psychology*, *39*, 15–22. http://doi.org/10.1080/00221309.1948.9918159

Blake, D. D., Weathers, F. W., Nagy, L. M., Kaloupek, D. G., Gusman, F. D., Charney, D. S., & Keane, T. M. (1995). The development of a Clinician-Administered PTSD Scale. *Journal of Traumatic Stress*, *8*(1), 75–90.

Block, S. R., & Liberzon, I. (2016). Attentional processes in posttraumatic stress disorder and the associated changes in neural functioning. *Experimental Neurology*, *284*, 153–167. http://doi.org/10.1016/j.expneurol.2016.05.009

Bluhm, R. L., Williamson, P. C., Osuch, E. A., Frewen, P. A., Stevens, T. K., Boksman, K., … Lanius, R. A. (2009). Alterations in default network connectivity in posttraumatic stress disorder related to early-life trauma. *Journal of Psychiatry and Neuroscience*, *34*(3), 187–194.

Boisgueheneuc, F. d., Levy, R., Volle, E., Seassau, M., Duffau, H., Kinkingnehun, S., … Dubois, B. (2006). Functions of the left superior frontal gyrus in humans: a lesion study. *Brain*, *129*(12), 3315–3328. http://doi.org/10.1093/brain/awl244

Botvinick, M., Braver, T., & Barch, D. (2001). Conflict monitoring and cognitive control. *Psychological Review*, *108*(3), 624–652. http://doi.org/10.1037/0033-295X.108.3.624

Botvinick, M., Cohen, J., & Carter, C. (2004). Conflict monitoring and anterior cingulate cortex: An update. *Trends Cogn Sci*, *8*(12), 539–546. http://doi.org/10.1007/s10548-006-0267-4

Braga, R. M., Wilson, L. R., Sharp, D. J., Wise, R. J. S., & Leech, R. (2013). Separable networks for top-down attention to auditory non-spatial and visuospatial modalities. *NeuroImage*, *74*, 77–86. http://doi.org/10.1016/j.neuroimage.2013.02.023

Brandes, D., Ben-Schachar, G., Gilboa, A., Bonne, O., Freedman, S., & Shalev, A. Y. (2002). PTSD symptoms and cognitive performance in recent trauma survivors. *Psychiatry Research*, *110*(3), 231–238. http://doi.org/10.1016/S0165-1781(02)00125-7

Bray, S., Arnold, A. E. G. F., Levy, R. M., & Iaria, G. (2015). Spatial and temporal functional connectivity changes between resting and attentive states. *Human Brain Mapping*, *36*(2),

549–565. http://doi.org/10.1002/hbm.22646

Bremner, J. D., Vermetten, E., & Vythilingam, M. (2004). Neural correlates of the classic color and emotional stroop inwomen with abuse-related posttraumatic stress disorder. *Biol. Psychiatry*, *55*, 612–620.

Brock, S. E., & Clinton, A. (2007). Diagnosis of Attention-Deficit / Hyperactivity Disorder (AD / HD) in Childhood : A Review of the Literature. *The California School Psychologist*, *12*, 73–91. http://doi.org/10.1037/a0032371

Brown, V. M., LaBar, K. S., Haswell, C. C., Gold, A. L., Beall, S. K., Van Voorhees, E., … Morey, R. A. (2014). Altered Resting-State Functional Connectivity of Basolateral and Centromedial Amygdala Complexes in Posttraumatic Stress Disorder. *Neuropsychopharmacology*, *39*(2), 361–369. http://doi.org/10.1038/npp.2013.197

Broyd, S. J., Demanuele, C., Debener, S., Helps, S. K., James, C. J., & Sonuga-Barke, E. J. S. (2009). Default-mode brain dysfunction in mental disorders: A systematic review. *Neuroscience & Biobehavioral Reviews*, *33*(3), 279–296. http://doi.org/10.1016/j.neubiorev.2008.09.002

Bryant, R. a, Felmingham, K. L., Kemp, a H., Barton, M., Peduto, a S., Rennie, C., … Williams, L. M. (2005). Neural networks of information processing in posttraumatic stress disorder: a functional magnetic resonance imaging study. *Biol Psychiatry*, *58*(2), 111–118. http://doi.org/10.1016/j.biopsych.2005.03.021

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network. *Annals of the New York Academy of Sciences*, *1124*(1), 1–38. http://doi.org/10.1196/annals.1440.011

Buckner, R. L., & Vincent, J. L. (2007). Unrest at rest: default activity and spontaneous network correlations. *NeuroImage*, *37*(4), 1091-6-9. http://doi.org/10.1016/j.neuroimage.2007.01.010

Burriss, L., Ayers, E., Ginsberg, J., & Powell, D. a. (2008). Learning and memory impairment in PTSD: relationship to depression. *Depression and Anxiety*, *25*(2), 149–57. http://doi.org/10.1002/da.20291

Callejas, A., Lupiàñez, J., Funes, M. J., & Tudela, P. (2005). Modulations among the alerting, orienting and executive control networks. *Experimental Brain Research*, *167*(1), 27–37. http://doi.org/10.1007/s00221-005-2365-z

Cao, Q., Zang, Y., Zhu, C., Cao, X., Sun, L., Zhou, X., & Wang, Y. (2008). Alerting deficits in children with attention deficit/hyperactivity disorder: event-related fMRI evidence. *Brain Research*, *1219*, 159–168. http://doi.org/10.1016/j.brainres.2008.04.028

Capote, H. A. (2009). Neuroimaging in Psychiatry. *Neurologic Clinics*, *27*(1), 237–249. http://doi.org/10.1016/j.ncl.2008.09.011

Casada, J. H., & Roache, J. D. (2005). Behavioral Inhibition and Activation in Posttraumatic Stress Disorder. *The Journal of Nervous and Mental Disease*, *193*(2), 102–109. http://doi.org/10.1097/01.nmd.0000152809.20938.37

Castellano, S., Ventimiglia, A., Salomone, S., Ventimiglia, A. J., De Vivo, S., Signorelli, M. S.,

… Caraci, F. (2016). Selective Serotonin Reuptake Inhibitors and Serotonin and Noradrenaline Reuptake Inhibitors improve cognitive function in partial responders depressed patients: results from a prospective observational cohort study. *CNS & Neurological Disorders Drug Targets*, *15*(10), 1290–1298. http://doi.org/10.2174/1871527315666161003170312

Centers for Disease Control and Prevention. (2013). CDC - Statistics - Traumatic Brain Injury - Injury Center. Retrieved from http://www.cdc.gov/traumaticbraininjury/statistics.html

Chun, M. M., & Turk-Browne, N. B. (2007). Interactions between attention and memory. *Current Opinion in Neurobiology*. http://doi.org/10.1016/j.conb.2007.03.005

Cisler, J. M., & Koster, E. H. W. (2010). Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clinical Psychology Review*, *30*(2), 203–16. http://doi.org/10.1016/j.cpr.2009.11.003

Clare Kelly, a. M., Uddin, L. Q., Biswal, B. B., Castellanos, F. X., & Milham, M. P. (2008). Competition between functional brain networks mediates behavioral variability. *NeuroImage*, *39*(1), 527–537. http://doi.org/10.1016/j.neuroimage.2007.08.008

Clausen, A. N., Francisco, A. J., Thelen, J., Bruce, J., Martin, L. E., McDowd, J., … Aupperle, R. L. (2017). PTSD and cognitive symptoms relate to inhibition-related prefrontal activation and functional connectivity. *Depression and Anxiety*. http://doi.org/10.1002/da.22613

Cocchi, L., Zalesky, A., Fornito, A., & Mattingley, J. B. (2013). Dynamic cooperation and competition between brain systems during cognitive control. *Trends Cogn Sci*, *17*(10), 493–501. http://doi.org/10.1016/j.tics.2013.08.006

Cole, M. W., Reynolds, J. R., Power, J. D., Repovs, G., Anticevic, A., & Braver, T. S. (2013). Multi-task connectivity reveals flexible hubs for adaptive task control. *Nature Neuroscience*, *16*(9), 1348–1355. http://doi.org/10.1038/nn.3470

Committee on the Assessment of Ongoing Efforts in the Treatment of Posttraumatic Stress Disorder, Board on the Health of Select Populations, & Institute of Medicine. (2014). *Access to Care*. National Academies Press (US). Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK224888/

Connor, K. M., Sutherland, S. M., Tupler, L. A., Malik, M. L., & Davidson, J. R. (1999). Fluoxetine in post-traumatic stress disorder. Randomised, double-blind study. *British Journal of Psychiatry*, *175*, 17–22.

Corbetta, M., Kincade, J. M., Ollinger, J. M., McAvoy, M. P., & Shulman, G. L. (2000). Voluntary orienting is dissociated from target detection in human posterior parietal cortex. *Nature Neuroscience*, *3*(3), 292–7. http://doi.org/10.1038/73009

Corbetta, M., Patel, G., & Shulman, G. L. (2008). The Reorienting System of the Human Brain: From Environment to Theory of Mind. *Neuron*, *58*(3), 306–324. http://doi.org/10.1016/j.neuron.2008.04.017

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews. Neuroscience*, *3*(3), 201–215. http://doi.org/10.1038/nrn755

Coull, J. T., Frith, C. D., Büchel, C., & Nobre, A. C. (2000). Orienting attention in time:

Behavioural and neuroanatomical distinction between exogenous and endogenous shifts. *Neuropsychologia*, *38*(6), 808–819. http://doi.org/10.1016/S0028-3932(99)00132-3

Crowell, T. a, Kieffer, K. M., Siders, C. a, & Vanderploeg, R. D. (2002). Neuropsychological findings in combat-related posttraumatic stress disorder. *The Clinical Neuropsychologist*, *16*(3), 310–21. http://doi.org/10.1076/clin.16.3.310.13851

Damoiseaux, J. S., Rombouts, S. A. R. B., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., & Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(37), 13848–53. http://doi.org/10.1073/pnas.0601417103

Danese, A., Moffitt, T. E., Arseneault, L., Bleiberg, B. A., Dinardo, P. B., Gandelman, S. B., … Caspi, A. (2017). The Origins of Cognitive Deficits in Victimized Children: Implications for Neuroscientists and Clinicians. *American Journal of Psychiatry*, *174*(4), 349–361. http://doi.org/10.1176/appi.ajp.2016.16030333

Daniels, J. K., McFarlane, A. C., Bluhm, R. L., Moores, K. A., Clark, C. R., Shaw, M. E., … Lanius, R. A. (2010). Switching between executive and default mode networks in posttraumatic stress disorder: alterations in functional connectivity. *Journal of Psychiatry & Neuroscience : JPN*, *35*(4), 258–66.

Daud, A., & Rydelius, P.-A. A. (2009). Comorbidity/overlapping between ADHD and PTSD in relation to IQ among children of traumatized/non-traumatized parents. *Journal of Attention Disorders*, *13*(2), 188–196. http://doi.org/10.1177/1087054708326271

De Bellis, M. D., Woolley, D. P., & Hooper, S. R. (2013). Neuropsychological findings in pediatric maltreatment: relationship of PTSD, dissociative symptoms, and abuse/neglect indices to neurocognitive outcomes. *Child Maltreatment*, *18*(3), 171–83. http://doi.org/10.1177/1077559513497420

de Haan, B., Morgan, P. S., & Rorden, C. (2008). Covert orienting of attention and overt eye movements activate identical brain regions. *Brain Research*, *1204*, 102–111. http://doi.org/10.1016/j.brainres.2008.01.105

De Luca, M., Beckmann, C. F., De Stefano, N., Matthews, P. M., & Smith, S. M. (2006). fMRI resting state networks define distinct modes of long-distance interactions in the human brain. *NeuroImage*, *29*(4), 1359–1367. http://doi.org/10.1016/j.neuroimage.2005.08.035

de Schotten, M. T., Dell'Acqua, F., Forkel, S. J., Simmons, A., Vergani, F., Murphy, D. G. M., & Catani, M. (2011). A lateralized brain network for visuospatial attention. *Nature Neuroscience*, *14*(10), 1245–1246. http://doi.org/10.1038/nn.2905

DiGangi, J. A., Tadayyon, A., Fitzgerald, D. A., Rabinak, C. A., Kennedy, A., Klumpp, H., … Phan, K. L. (2016). Reduced default mode network connectivity following combat trauma. *Neuroscience Letters*, *615*, 37–43. http://doi.org/10.1016/j.neulet.2016.01.010

Dosenbach, N. U. F., Fair, D. A., Cohen, A. L., Schlaggar, B. L., & Petersen, S. E. (2008). A dual-networks architecture of top-down control. *Trends in Cognitive Sciences*, *12*(3), 99–105. http://doi.org/10.1016/j.tics.2008.01.001

Doucet, G., Naveau, M., Petit, L., Zago, L., Crivello, F., Jobard, G., … Joliot, M. (2012).

Patterns of hemodynamic low-frequency oscillations in the brain are modulated by the nature of free thought during rest. *NeuroImage*, *59*(4), 3194–3200. http://doi.org/10.1016/j.neuroimage.2011.11.059

Duann, J.-R., Ide, J. S., Luo, X., & Li, C. R. (2009). Functional connectivity delineates distinct roles of the inferior frontal cortex and presupplementary motor area in stop signal inhibition. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *29*(32), 10171–9. http://doi.org/10.1523/JNEUROSCI.1300-09.2009

Duval, E. R., Javanbakht, A., & Liberzon, I. (2015). Neural circuits in anxiety and stress disorders: a focused review. *Therapeutics and Clinical Risk Management*, *11*, 115–26. http://doi.org/10.2147/TCRM.S48528

El Khoury-Malhame, M., Reynaud, E., Soriano, A., Michael, K., Salgado-Pineda, P., Zendjidjian, X., … Khalfa, S. (2011). Amygdala activity correlates with attentional bias in PTSD. *Neuropsychologia*, *49*(7), 1969–1973. http://doi.org/10.1016/j.neuropsychologia.2011.03.025

Elton, A., & Gao, W. (2014). Divergent task-dependent functional connectivity of executive control and salience networks. *Cortex*, *51*(1), 56–66. http://doi.org/10.1016/j.cortex.2013.10.012

Elton, A., & Gao, W. (2015). Task-positive Functional Connectivity of the Default Mode Network Transcends Task Domain. *Journal of Cognitive Neuroscience*, *27*(12), 2369–2381. http://doi.org/10.1162/jocn_a_00859

Eren-Kocak, E., Kilic, C., Aydin, I., & Hizli, F. G. (2009). Memory and prefrontal functions in earthquake survivors: Differences between current and past post-traumatic stress disorder patients. *Acta Psychiatrica …*, *119*(1), 35–44. http://doi.org/10.1111/j.1600-0447.2008.01281.x

Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & Psychophysics*, *16*(1), 143–149. http://doi.org/10.3758/BF03203267

Etkin, A., & Wager, T. D. (2007). Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *The American Journal of Psychiatry*, *164*(10), 1476–88. http://doi.org/10.1176/appi.ajp.2007.07030504

Everitt, B. J., & Robbins, T. W. (1997). Central cholinergic systems and cognition. *Annual Review of Psychology*, *48*, 649–684. http://doi.org/10.1146/annurev.psych.48.1.649

Fair, D. A., Nigg, J. T., Iyer, S., Bathula, D., Mills, K. L., Dosenbach, N. U. F., … Milham, M. P. (2012). Distinct neural signatures detected for ADHD subtypes after controlling for micro-movements in resting state functional connectivity MRI data. *Frontiers in Systems Neuroscience*, *6*, 80. http://doi.org/10.3389/fnsys.2012.00080

Falconer, E., Allen, A., Felmingham, K. L., Williams, L. M., & Bryant, R. A. (2013). Inhibitory neural activity predicts response to cognitive-behavioral therapy for posttraumatic stress disorder. *Journal of Clinical Psychiatry*, *74*(9), 895–901. http://doi.org/10.4088/JCP.12m08020

Falconer, E., Bryant, R., Felmingham, K. L., Kemp, A. H., Gordon, E., Peduto, A., … Williams, L. M. (2008). The neural networks of inhibitory control in posttraumatic stress disorder. *Journal of Psychiatry & Neuroscience*, *33*(3), 413–422.

Fan, J. (2014). An information theory account of cognitive control. *Frontiers in Human Neuroscience*, *8*, 680. http://doi.org/10.3389/fnhum.2014.00680

Fan, J., Byrne, J., Worden, M. S., Guise, K. G., McCandliss, B. D., Fossella, J., & Posner, M. I. (2007). The Relation of Brain Oscillations to Attentional Networks. *Journal of Neuroscience*, *27*(23), 6197–6206. http://doi.org/10.1523/JNEUROSCI.1833-07.2007

Fan, J., Fossella, J., Sommer, T., Wu, Y., & Posner, M. I. (2003). Mapping the genetic variation of executive attention onto brain activity. *Proceedings of the National Academy of Sciences of the United States of America*, *100*, 7406–7411. http://doi.org/10.1073/pnas.0732088100

Fan, J., Gu, X., Guise, K. G., Liu, X., Fossella, J., Wang, H., & Posner, M. I. (2009). Testing the behavioral interaction and integration of attentional networks. *Brain and Cognition*, *70*(2), 209–220. http://doi.org/10.1016/j.bandc.2009.02.002

Fan, J., Hof, P. R., Guise, K. G., Fossella, J. A., & Posner, M. I. (2008). The functional integration of the anterior cingulate cortex during conflict processing. *Cerebral Cortex*, *18*(4), 796–805. http://doi.org/10.1093/cercor/bhm125

Fan, J., McCandliss, B. D., Fossella, J., Flombaum, J. I., & Posner, M. I. (2005). The activation of attentional networks. *NeuroImage*, *26*(2), 471–479. http://doi.org/10.1016/j.neuroimage.2005.02.004

Fan, J., McCandliss, B. D., Sommer, T., Raz, A., & Posner, M. I. (2002). Testing the efficiency and independence of attentional networks. *Journal of Cognitive Neuroscience*, *14*(3), 340–347.

Fan, J., & Posner, M. I. (2004). Human Attentional Networks. *Bibliografie Psychiat Prax*, *31*(2), 210–214. http://doi.org/10.1055/s-2004-828484

Felmingham, K. L., Williams, L. M., Kemp, A. H., Rennie, C., Gordon, E., & Bryant, R. A. (2009). Anterior cingulate activity to salient stimuli is modulated by autonomic arousal in Posttraumatic Stress Disorder. *Psychiatry Research - Neuroimaging*, *173*(1), 59–62. http://doi.org/10.1016/j.pscychresns.2008.12.005

Fernandez-Duque, D., & Posner, M. I. (1997). Relating the mechanisms of orienting and alerting. *Neuropsychologia*, *35*(4), 477–486. http://doi.org/10.1016/S0028-3932(96)00103-0

Fischer, E. H., Dornelas, E. A., & Goethe, J. W. (2001). Characteristics of people lost to attrition in psychiatric follow-up studies. *The Journal of Nervous and Mental Disease*, *189*(1), 49–55. http://doi.org/11206665

Fossella, J., Sommer, T., Fan, J., Wu, Y., Swanson, J. M., Pfaff, D. W., & Posner, M. I. (2002). Assessing the molecular genetics of attention networks. *BMC Neuroscience*, *3*, 14. http://doi.org/10.1186/1471-2202-3-14

Fox, M. D., Corbetta, M., Snyder, A. Z., Vincent, J. L., & Raichle, M. E. (2006). Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(26), 10046–10051.

Fox, M. D., & Greicius, M. (2010). Clinical applications of resting state functional connectivity. *Frontiers in Systems Neuroscience*, *4*, 19. http://doi.org/10.3389/fnsys.2010.00019

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(27), 9673–9678.

Frewen, P. A., & Lanius, R. A. (2006). Toward a psychobiology of posttraumatic self-dysregulation: Reexperiencing, hyperarousal, dissociation, and emotional numbing. *Annals of the New York Academy of Sciences*, *1071*(PSYCHOBIOLOGY OF POSTTRAUMATIC STRESS DISORDER A Decade of Progress), 110–124. http://doi.org/10.1196/annals.1364.010

Gamboz, N., Zamarian, S., & Cavallero, C. (2010). Age-Related Differences in the Attention Network Test (ANT). *Experimental Aging Research*, *36*(3), 287–305. http://doi.org/10.1080/0361073X.2010.484729

Garner, M., Attwood, A., Baldwin, D. S., & Munafò, M. R. (2012). Inhalation of 7.5% carbon dioxide increases alerting and orienting attention network function. *Psychopharmacology*, *223*(1), 67–73. http://doi.org/10.1007/s00213-012-2690-4

Gerin, M. I., Fichtenholtz, H., Roy, A., Walsh, C. J., Krystal, J. H., Southwick, S., & Hampson, M. (2016). Real-Time fMRI Neurofeedback with War Veterans with Chronic PTSD: A Feasibility Study. *Frontiers in Psychiatry*, *7*, 111. http://doi.org/10.3389/fpsyt.2016.00111

Gil, T., Calev, A., Greenberg, D., & Kugelmass, S. (1990). Cognitive functioning in post-traumatic stress disorder. *Journal of Traumatic Stress*, *3*(1), 29–45. http://doi.org/10.1007/BF00975134

Gilbertson, M. W., Paulus, L. A., Williston, S. K., Gurvits, T. V., Lasko, N. B., Pitman, R. K., & Orr, S. P. (2006). Neurocognitive function in monozygotic twins discordant for combat exposure: Relationship to posttraumatic stress disorder. *Journal of Abnormal Psychology*, *115*(3), 484–495. http://doi.org/10.1037/0021-843X.115.3.484

Golier, J., Yehuda, R., Cornblatf, B., & Harvey, P. (1997). Sustained Attention in Combat-related Posttraumatic Stress Disorder, *32*(1), 52–61.

Gong, Q., Li, L., Du, M., Pettersson-Yeo, W., Crossley, N., Yang, X., … Mechelli, A. (2014). Quantitative prediction of individual psychopathology in trauma survivors using resting-state FMRI. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *39*(3), 681–7. http://doi.org/10.1038/npp.2013.251

Gooding, D. C., Braun, J. G., & Studer, J. A. (2006). Attentional network task performance in patients with schizophrenia-spectrum disorders: Evidence of a specific deficit. *Schizophrenia Research*, *88*(1–3), 169–178. http://doi.org/10.1016/j.schres.2006.07.009

Gray, R. (2006). Comprehensive Trail Making Test. *Journal of Psychoeducational Assessment*, *24*(1), 88–91. http://doi.org/10.1177/0734282905282415

Green, A. E., Munafò, M. R., Deyoung, C. G., Fossella, J. a, Fan, J., & Gray, J. R. (2008). Using genetic data in cognitive neuroscience: from growing pains to genuine insights. *Nature*

Reviews Neuroscience, *9*, 710–720. http://doi.org/10.1038/nrn2461

Green, B. L., Krupnick, J. L., Stockton, P., Goodman, L., Corcoran, C., & Petty, R. (2005). Effects of adolescent trauma exposure on risky behavior in college women. *Psychiatry*, *68*(4), 363–378. http://doi.org/10.1521/psyc.2005.68.4.363

Greenberg, A. S., Verstynen, T., Chiu, Y.-C., Yantis, S., Schneider, W., & Behrmann, M. (2012). Visuotopic Cortical Connectivity Underlying Attention Revealed with White-Matter Tractography. *Journal of Neuroscience*, *32*(8), 2773–2782. http://doi.org/10.1523/JNEUROSCI.5419-11.2012

Greene, D. J., Barnea, A., Herzberg, K., Rassis, A., Neta, M., Raz, A., & Zaidel, E. (2008). Measuring attention in the hemispheres: the lateralized attention network test (LANT). *Brain and Cognition*, *66*(1), 21–31. http://doi.org/10.1016/j.bandc.2007.05.003

Greicius, M. (2008). Resting-state functional connectivity in neuropsychiatric disorders. *Current Opinion in Neurology*, *21*(4), 424–30. http://doi.org/10.1097/WCO.0b013e328306f2c5

Guo, C. C., Kurth, F., Zhou, J., Mayer, E. A., Eickhoff, S. B., Kramer, J. H., & Seeley, W. W. (2012). One-year test–retest reliability of intrinsic connectivity network fMRI in older adults. *NeuroImage*, *61*(4), 1471–1483. http://doi.org/10.1016/j.neuroimage.2012.03.027

Hahn, B., Ross, T. J., & Stein, E. a. (2006). Neuroanatomical dissociation between bottom-up and top-down processes of visuospatial selective attention. *NeuroImage*, *32*(2), 842–853. http://doi.org/10.1016/j.neuroimage.2006.04.177

Hahn, J. W., Aldarondo, E., Silverman, J. G., McCormick, M. C., & Koenen, K. C. (2015). Examining the Association between Posttraumatic Stress Disorder and Intimate Partner Violence Perpetration. *Journal of Family Violence*, *30*(6), 743–752. http://doi.org/10.1007/s10896-015-9710-1

Hampson, M., Hampson, M., Driesen, N. N. R., Driesen, N. N. R., Skudlarski, P., Skudlarski, P., … Jc. (2006). Brain connectivity related to working memory performance. *Journal of Neuroscience*, *26*(51), 13338–13343. http://doi.org/10.1523/JNEUROSCI.3408-06.2006.Brain

Harrison, B. J., Shaw, M., Yucel, M., Purcell, R., Brewer, W. J., Strother, S. C., … Pantelis, C. (2005). Functional connectivity during Stroop task performance. *Neuroimage*, *24*(1), 181–191. http://doi.org/10.1016/j.neuroimage.2004.08.033

Hart, J., Kimbrell, T., Fauver, P., Cherry, B. J., Pitcock, J., Booe, L. Q., … Freeman, T. W. (2008, July 1). Cognitive dysfunctions associated with PTSD: evidence from World War II prisoners of war. *The Journal of Neuropsychiatry and Clinical Neurosciences*. American Psychiatric Publishing, Inc. http://doi.org/10.1176/appi.neuropsych.20.3.309

Hembree, E. a., Foa, E. B., Dorfan, N. M., Street, G. P., Kowalski, J., & Tu, X. (2003). Do Patients Drop Out Prematurely from Exposure Therapy for PTSD? *Journal of Traumatic Stress*, *16*(6), 555–562. http://doi.org/10.1023/B:JOTS.0000004078.93012.7d

Horner, M. D., & Hamner, M. B. (2002). Neurocognitive functioning in posttraumatic stress disorder. *Neuropsychology Review*, *12*(1), 15–30. http://doi.org/10.1023/A

Ipser, J., Seedat, S., & Stein, D. J. (2006). Pharmacotherapy for post-traumatic stress disorder - a

systematic review and meta-analysis. *South African Medical Journal*, *96*(10), 1088–96.

Jakupcak, M., Conybeare, D., Phelps, L., Hunt, S., Holmes, H. A., Felker, B., … McFall, M. E. (2007). Anger, hostility, and aggression among Iraq and Afghanistan war veterans reporting PTSD and subthreshold PTSD. *Journal of Traumatic Stress*, *20*(6), 945–954. http://doi.org/10.1002/jts.20258

James, W. (1890). The principles of psychology (Vols. 1 & 2). *New York Holt*, *118*, 688. http://doi.org/10.1037/10538-000

Jenkins, M. A., Langlais, P. J., Delis, D., Cohen, R. A., Jenkins, M. A., Langlais, P. J., … Cohen, R. A. (2010). Attentional Dysfunction Associated with Posttraumatic Stress Disorder Among Rape Survivors. *The Clinical Neuropsychologist*, *14*(1), 7–12. http://doi.org/10.1076/1385-4046(200002)14

Jennings, J. M., Dagenbach, D., Engle, C. M., & Funke, L. J. (2007). Age-related changes and the attention network task: an examination of alerting, orienting, and executive function. *Neuropsychology, Development, and Cognition. Section B, Aging, Neuropsychology and Cognition*, *14*(4), 353–69. http://doi.org/10.1080/13825580600788837

Jilka, S. R., Scott, G., Ham, T., Pickering, A., Bonnelle, V., Braga, R. M., … Sharp, D. J. (2014). Damage to the Salience Network and Interactions with the Default Mode Network. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *34*(33), 10798–10807. http://doi.org/10.1523/JNEUROSCI.0518-14.2014

Johnsen, G. E., & Asbjørnsen, A. E. (2008). Consistent impaired verbal memory in PTSD: a meta-analysis. *Journal of Affective Disorders*, *111*(1), 74–82. http://doi.org/10.1016/j.jad.2008.02.007

Jovanovic, T., Kazama, A., Bachevalier, J., & Davis, M. (2012). Impaired safety signal learning may be a biomarker of PTSD. *Neuropharmacology*. http://doi.org/10.1016/j.neuropharm.2011.02.023

Kanagaratnam, P., & Asbjørnsen, A. E. (2007). Executive deficits in chronic PTSD related to political violence. *Journal of Anxiety Disorders*, *21*(4), 510–25. http://doi.org/10.1016/j.janxdis.2006.06.008

Ke, J., Zhang, L., Qi, R., Li, W., Hou, C., Zhong, Y., … Lu, G. (2016). A longitudinal fMRI investigation in acute post-traumatic stress disorder (PTSD). *Acta Radiol*, *57*(11), 1387–1395. http://doi.org/10.1177/0284185115585848

Kennis, M., Rademaker, A. R., van Rooij, S. J. H., Kahn, R. S., & Geuze, E. (2015). Resting state functional connectivity of the anterior cingulate cortex in veterans with and without post-traumatic stress disorder. *Human Brain Mapping*, *36*(1), 99–109. http://doi.org/10.1002/hbm.22615

Kennis, M., van Rooij, S. J. H., van den Heuvel, M. P., Kahn, R. S., & Geuze, E. (2016). Functional network topology associated with posttraumatic stress disorder in veterans. *NeuroImage. Clinical*, *10*, 302–9. http://doi.org/10.1016/j.nicl.2015.12.008

Kessler, R. C., Sonnega, A., Bromet, E., Hughes, M., & Nelson, C. B. (1995). Posttraumatic stress disorder in the National Comorbidity Survey. *Archives of General Psychiatry*, *52*(12),

1048–60.

Kilpatrick, D. G., Resnick, H. S., Milanak, M. E., Miller, M. W., Keyes, K. M., & Friedman, M. J. (2013). National Estimates of Exposure to Traumatic Events and PTSD Prevalence Using DSM-IV and DSM-5 Criteria. *Journal of Traumatic Stress*, *26*(5), 537–547. http://doi.org/10.1002/jts.21848

Kimbrel, N. A., Johnson, M. E., Clancy, C., Hertzberg, M., Collie, C., Van Voorhees, E. E., … Beckham, J. C. (2014). Deliberate self-harm and suicidal ideation among male Iraq/Afghanistan-era veterans seeking treatment for PTSD. *Journal of Traumatic Stress*, *27*(4), 474–477. http://doi.org/10.1002/jts.21932

King, A. P., Block, S. R., Sripada, R. K., Rauch, S. A. M., Porter, K. E., Favorite, T. K., … Liberzon, I. (2016). A Pilot Study of Mindfulness-Based Exposure Therapy in OEF/OIF Combat Veterans with PTSD: Altered Medial Frontal Cortex and Amygdala Responses in Social–Emotional Processing. *Frontiers in Psychiatry*, *7*, 154. http://doi.org/10.3389/FPSYT.2016.00154

King, A. P., Block, S. R., Sripada, R. K., Rauch, S., Giardino, N., Favorite, T., … Liberzon, I. (2016). Altered Default Mode Network (Dmn) Resting State Functional Connectivity Following a Mindfulness-Based Exposure Therapy for Posttraumatic Stress Disorder (Ptsd) in Combat Veterans of Afghanistan and Iraq. *Depression and Anxiety*, *33*(4), 289–299. http://doi.org/10.1002/da.22481

Kivling-Bodén, G., & Sundbom, E. (2003). Cognitive abilities related to post-traumatic symptoms among refugees from the former Yugoslavia in psychiatric treatment. *Nordic Journal of Psychiatry*, *57*(3), 191–198. http://doi.org/10.1080/08039480310001346

Klein, R. M. (2000). Inhibition of return. *Trends in Cognitive Sciences*. http://doi.org/10.1016/S1364-6613(00)01452-2

Koenen, K. C., Driver, K. L., Oscar-Berman, M., Wolfe, J., Folsom, S., Huang, M. T., & Schlesinger, L. (2001). Measures of prefrontal system dysfunction in posttraumatic stress disorder. *Brain and Cognition*, *45*(1), 64–78. http://doi.org/10.1006/brcg.2000.1256

Koike, T., Kan, S., Misaki, M., & Miyauchi, S. (2011). Connectivity pattern changes in default-mode network with deep non-REM and REM sleep. *Neuroscience Research*, *69*(4), 322–330. http://doi.org/10.1016/j.neures.2010.12.018

Koso, M., & Hansen, S. (2006). Executive function and memory in posttraumatic stress disorder: a study of Bosnian war veterans. *European Psychiatry : The Journal of the Association of European Psychiatrists*, *21*(3), 167–73. http://doi.org/10.1016/j.eurpsy.2005.06.004

Koso, M., Sarač-Hadzihalilovic, A., & Hansen, S. (2012). Neuropsychological performance, psychiatric symptoms, and everyday cognitive failures in Bosnian ex-servicemen with posttraumatic stress disorder. *Review of Psychology*, *19*(2), 131–139.

Kram, M., Rushwort, M. F. S., Frackowiak, R. S. J., Passingham, R. E., & Rushworth, M. F. S. (1998). The preparation, execution and suppression of copied movements in the human brain. *Exp Brain Res*, *120*, 386–398.

Krikorian, R., Bartok, J., Gay, N., & Anonymous. (1994). Tower-Of-London Procedure - a

Standard Method and Developmental-Data. *Journal of Clinical and Experimental Neuropsychology*, *16*(6), 840–850.

Kucyi, a., Hodaie, M., & Davis, K. D. (2012). Lateralization in intrinsic functional connectivity of the temporoparietal junction with salience- and attention-related brain networks. *Journal of Neurophysiology*, *108*(12), 3382–92. http://doi.org/10.1152/jn.00674.2012

Lagarde, G., Doyon, J., & Brunet, A. (2010). Memory and executive dysfunctions associated with acute posttraumatic stress disorder. *Psychiatry Research*, *177*(1–2), 144–9. http://doi.org/10.1016/j.psychres.2009.02.002

Lanius, R. A., Bluhm, R. L., Coupland, N. J., Hegadoren, K. M., Rowe, B., Théberge, J., … Brimson, M. (2010). Default mode network connectivity as a predictor of post-traumatic stress disorder symptom severity in acutely traumatized subjects. *Acta Psychiatrica Scandinavica*, *121*(1), 33–40. http://doi.org/10.1111/j.1600-0447.2009.01391.x

Lanius, R. A., Bluhm, R. L., Coupland, N. J., Hegadoren, K. M., Rowe, B., Théberge, J., … Brimson, M. (2010). Default mode network connectivity as a predictor of post-traumatic stress disorder symptom severity in acutely traumatized subjects. *Acta Psychiatrica Scandinavica*, *121*(1), 33–40. http://doi.org/10.1111/j.1600-0447.2009.01391.x

Lapham, S. C., C'de Baca, J., McMillan, G. P., & Lapidus, J. (2006). Psychiatric disorders in a sample of repeat impaired-driving offenders. *Journal of Studies on Alcohol*, *67*(5), 707–713.

Leark, R. A., Dupuy, T. R., Greenberg, L. M., Kindschi, C. L., & Hughes, S. J. (2016). Test Of Variables of Attention Continuous Performance Test. *Edition Number*, *8*(8). Retrieved from http://www.tovatest.com/

Leskin, L. P., & White, P. M. (2007). Attentional networks reveal executive function deficits in posttraumatic stress disorder. *Neuropsychology*, *21*(3), 275–284. http://doi.org/10.1037/0894-4105.21.3.275

Levy-Gigi, E., Richter-Levin, G., Okon-Singer, H., Kéri, S., & Bonanno, G. A. (2016). The hidden price and possible benefit of repeated traumatic exposure. *Stress*, *19*(1), 1–7. http://doi.org/10.3109/10253890.2015.1113523

Lew, H. L., Kraft, M., Pogoda, T. K., Amick, M. M., Woods, P., & Cifu, D. X. (2011). Prevalence and characteristics of driving difficulties in Operation Iraqi Freedom/Operation Enduring Freedom combat returnees. *Journal of Rehabilitation Research and Development*, *48*(8), 913–925. http://doi.org/Doi 10.1682/Jrrd.2010.08.0140

Liberzon, I., & Abelson, J. L. (2016). Context Processing and the Neurobiology of Post-Traumatic Stress Disorder. *Neuron*, *92*(1), 14–30. http://doi.org/10.1016/j.neuron.2016.09.039

Lindauer, R. J. L. R. J. L., Olff, M., van Meijel, E. P. M., Carlier, I. V. E., Gersons, B. P. R., Olff, M., & van Meijel, E. P. M. (2006). Cortisol, learning, memory, and attention in relation to smaller hippocampal volume in police officers with posttraumatic stress disorder. *Biological Psychiatry*, *59*, 171–177. http://doi.org/10.1016/j.biopsych.2005.06.033

Liu, Y., Li, L., Li, B., Zhang, X., & Lu, H. (2017). Decreased triple network connectivity in patients with post-traumatic stress disorder. In A. Krol & B. Gimi (Eds.), (p. 101370Q).

International Society for Optics and Photonics. http://doi.org/10.1117/12.2254367

Lockwood, E., & Forbes, D. (2014). Posttraumatic Stress Disorder and Comorbidity: Untangling the Gordian Knot. *Psychological Injury and Law*, *7*(2), 108–121. http://doi.org/10.1007/s12207-014-9189-8

Lu, H. B., Zou, Q. H., Gu, H., Raichle, M. E., Stein, E. A., & Yang, Y. H. (2012). Rat brains also have a default mode network. *Proceedings of the*, *109*, 3979–3984.

Lund, T. E., Madsen, K. H., Sidaros, K., Luo, W.-L., & Nichols, T. E. (2006). Non-white noise in fMRI: does modelling have an impact? *NeuroImage*, *29*(1), 54–66. http://doi.org/10.1016/j.neuroimage.2005.07.005

Luxenberg, T., Spinazzola, J., Van Der Kolk, B. A., Hidalgo, J., & Hunt, C. (2001). Complex Trauma and Disorders of Extreme Stress (DESNOS) Diagnosis, Part One: Assessment. *Directions in Psychiatry*, *21*, 373–393.

Macleod, J. W., Lawrence, M. A., McConnell, M. M., Eskes, G. A., Klein, R. M., & Shore, D. I. (2010). Appraising the ANT: Psychometric and theoretical considerations of the Attention Network Test. *Neuropsychology*, *24*(5), 637–651. http://doi.org/10.1037/a0019803

Madhyastha, T. M., Askren, M. K., Boord, P., & Grabowski, T. J. (2015). Dynamic connectivity at rest predicts attention task performance. *Brain Connectivity*, *5*(1), 45–59. http://doi.org/10.1089/brain.2014.0248

Madhyastha, T. M., & Grabowski, T. J. (2014). Age-related differences in the dynamic architecture of intrinsic networks. *Brain Connectivity*, *4*(4), 231–41. http://doi.org/10.1089/brain.2013.0205

Madu, S. N., & Peltzer, K. (2000). Neurologic soft signs in chronic posttraumatic stress disorder. *Arch Gen Psychiatry*, *57*(2), 181–186.

Maldjian, J., Laurienti, P. J., & Burdette, J. H. (2004). Precentral gyrus discrepancy in electronic versions of the Talairach atlas. *NeuroImage*, *21*(1), 450–455. http://doi.org/10.1016/j.neuroimage.2003.09.032

Maldjian, J., Laurienti, P. J., Kraft, R. A., & Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *NeuroImage*, *19*(3), 1233–1239. http://doi.org/10.1016/S1053-8119(03)00169-1

Manelis, a., & Reder, L. M. (2012). Procedural learning and associative memory mechanisms contribute to contextual cueing: Evidence from fMRI and eye-tracking. *Learning & Memory*, *19*(11), 527–534. http://doi.org/10.1101/lm.025973.112

Mantini, D., Gerits, A., Nelissen, K., Durand, J.-B., Joly, O., Simone, L., … Vanduffel, W. (2011). Default mode of brain function in monkeys. *J Neurosci*, *31*(36), 12954–12962. http://doi.org/10.1523/JNEUROSCI.2318-11.2011

Markett, S., Reuter, M., Montag, C., Voigt, G., Lachmann, B., Rudorf, S., … Weber, B. (2014). Assessing the function of the fronto-parietal attention network: Insights from resting-state fMRI and the attentional network test. *Human Brain Mapping*, *35*(4), 1700–1709. http://doi.org/10.1002/hbm.22285

Marrocco, R., & Davidson, M. (1998). Neurochemistry of attention. In *The Attentive Brain* (pp. 35–50). http://doi.org/http://dx.doi.org/10.1016/S1364-6613(98)01245-5

McAllister, T. W., Zafonte, R., Jain, S., Flashman, L. A., George, M. S., Grant, G. A., … Stein, M. B. (2016). Randomized Placebo-Controlled Trial of Methylphenidate or Galantamine for Persistent Emotional and Cognitive Symptoms Associated with PTSD and/or Traumatic Brain Injury. *Neuropsychopharmacology*, *41*(5), 1191–1198. http://doi.org/10.1038/npp.2015.282

McFarlane, A. C., Weber, D. L., & Clark, C. R. (1993). Abnormal stimulus processing in posttraumatic stress disorder. *Biological Psychiatry*, *34*(5), 311–320. http://doi.org/10.1016/0006-3223(93)90088-U

McIntyre, R. S., Harrison, J., Loft, H., Jacobson, W., & Olsen, C. K. (2016). The Effects of Vortioxetine on Cognitive Function in Patients with Major Depressive Disorder (MDD): a Meta-Analysis of Three Randomized Controlled Trials. *The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*, *19*, 1–9. http://doi.org/10.1093/ijnp/pyw055

Mennes, M., Kelly, C., Zuo, X.-N., Di Martino, A., Biswal, B. B., Castellanos, F. X., & Milham, M. P. (2010). Inter-individual differences in resting-state functional connectivity predict task-induced BOLD activity. *NeuroImage*, *50*(4), 1690–701. http://doi.org/10.1016/j.neuroimage.2010.01.002

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure and Function*, *214*(5–6), 1–13. http://doi.org/10.1007/s00429-010-0262-0

Messinger, S. D. (2013). Vigilance and attention among U.S. service members and veterans after combat. *Anthropology of Consciousness*, *24*(2), 191–207. http://doi.org/10.1111/anoc.12013

Miller, D. R., Hayes, S. M., Hayes, J. P., Spielberg, J. M., Lafleche, G., & Verfaellie, M. (2017). Default Mode Network Subsystems Are Differentially Disrupted in Posttraumatic Stress Disorder. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. http://doi.org/10.1016/j.bpsc.2016.12.006

Miller, J. L., James, G. a., Goldstone, a. P., Couch, J. a, He, G., Driscoll, D. J., & Liu, Y. (2007). Enhanced activation of reward mediating prefrontal regions in response to food stimuli in Prader-Willi syndrome. *Journal of Neurology, Neurosurgery & Psychiatry*, *78*(6), 615–619. http://doi.org/10.1136/jnnp.2006.099044

Miotto, E. C., Cinalli, F. Z., Serrao, V. T., Benute, G. G., Lucia, M. C. S., & Scaff, M. (2010). Cognitive deficits in patients with mild to moderate traumatic brain injury. *Arquivos de Neuro-Psiquiatria*, *68*(6), 862–868. http://doi.org/10.1590/S0004-282X2010000600006

Monastra, V. J. (2008). Unlocking the potential of patients with ADHD: a model for clinical practice. *Archives of Clinical Neuropsychology*, *23*(3), 360:362.

Morcom, A. M., & Fletcher, P. C. (2007). Does the brain have a baseline? Why we should be resisting a rest. *NeuroImage*, *37*(4), 1073–82. http://doi.org/10.1016/j.neuroimage.2007.06.019

Muto, V., Shaffii-Le Bourdiec, A., Matarazzo, L., Foret, A., Mascetti, L., Jaspar, M., … Maquet, P. (2012). Influence of acute sleep loss on the neural correlates of alerting, orientating and executive attention components. *Journal of Sleep Research*, *21*(6), 648–658. http://doi.org/10.1111/j.1365-2869.2012.01020.x

Nagane, A., Baba, H., Nakano, Y., Maeshima, H., Hukatsu, M., Ozawa, K., … Arai, H. (2014). Comparative study of cognitive impairment between medicated and medication-free patients with remitted major depression: Class-specific influence by tricyclic antidepressants and newer antidepressants. *Psychiatry Research*, *218*(1–2), 101–105. http://doi.org/10.1016/j.psychres.2014.04.013

Netto, L. R., Pereira, J. L., Nogueira, J. F., Cavalcanti-Ribeiro, P., Santana, R. C., Teles, C. A., … Quarantini, L. C. (2016). Impulsivity is relevant for trauma exposure and PTSD symptoms in a non-clinical population. *Psychiatry Research*, *239*, 204–211. http://doi.org/10.1016/j.psychres.2016.03.027

Neylan, T.-C., Lenoci, M., Rothlind, J., Metzler, T.-J., Schuff, N., Du, A.-T. T., … Marmar, C.-R. (2004). Attention, learning, and memory in posttraumatic stress disorder. *J Trauma Stress*, *17*, 41–46. http://doi.org/10.1023/B:JOTS.0000014675.75686.ee

Nicholson, A. A., Sapru, I., Densmore, M., Frewen, P. A., Neufeld, R. W. J., Théberge, J., … Lanius, R. A. (2016). Unique insula subregion resting-state functional connectivity with amygdala complexes in posttraumatic stress disorder and its dissociative subtype. *Psychiatry Research - Neuroimaging*, *250*, 61–72. http://doi.org/10.1016/j.pscychresns.2016.02.002

Norris, F. H. (1992). Epidemiology of trauma: frequency and impact of different potentially traumatic events on different demographic groups. *Journal of Consulting and Clinical Psychology*, *60*(3), 409–18.

Ollinger, J. M., Shulman, G. L., & Corbetta, M. (2001). Separating processes within a trial in event-related functional MRI. I. The Method. *Neuroimage*, *13*(1), 210–217. http://doi.org/10.1006/nimg.2000.0710

Pacheco-Unguetti, A. P., Acosta, A., Marqués, E., & Lupiáñez, J. (2011). Alterations of the attentional networks in patients with anxiety disorders. *Journal of Anxiety Disorders*, *25*(7), 888–895. http://doi.org/10.1016/j.janxdis.2011.04.010

Pannu Hayes, J., LaBar, K. S., Petty, C. M., McCarthy, G., & Morey, R. a. (2009). Alterations in the neural circuitry for emotion and attention associated with posttraumatic stress symptomatology. *Psychiatry Research - Neuroimaging*, *172*(1), 7–15. http://doi.org/10.1016/j.pscychresns.2008.05.005

Parslow, R. A., & Jorm, A. F. (2007). Pretrauma and Posttrauma Neurocognitive Functioning and PTSD Symptoms in a Community Sample of Young Adults. *Am J Psychiatry*, *164*(3), 509–515. http://doi.org/10.1176/appi.ajp.164.3.509

Patros, C. H. G., Matt Alderson, R., Kasper, L. J., Tarle, S. J., Lea, S. E., & Hudec, K. L. (2015). Choice-impulsivity in children and adolescents with attention-deficit/hyperactivity disorder (ADHD): A meta-analytic review. *Clinical Psychology Review*. http://doi.org/10.1016/j.cpr.2015.11.001

Patterson, K., & Plaut, D. C. (2009). "Shallow Draughts Intoxicate the Brain": Lessons from Cognitive Science for Cognitive Neuropsychology. *Topics in Cognitive Science*, *1*(1), 39–58. http://doi.org/10.1111/j.1756-8765.2008.01012.x

Pavlovskaya, M., Groswasser, Z., Keren, O., Mordvinov, E., & Hochstein, S. (2007). Hemispheric visual atentional imbalance in patients with traumatic brain injury. *Brain and Cognition*, *64*(1), 21–29. http://doi.org/10.1016/j.bandc.2006.10.003

Perry, R. J., & Hodges, J. R. (1999). Attention and executive deficits in Alzheimer's disease. A critical review. *Brain*. http://doi.org/10.1093/brain/122.3.383

Petersen, & Posner. (2012). The attention system of the human brain: 20 years after. *Annual Review of Neuroscience*, *35*, 73–89. http://doi.org/10.1146/annurev-neuro-062111-150525

Philip, N. S., Sweet, L. H., Tyrka, A. R., Carpenter, S. L., Albright, S. E., Price, L. H., & Carpenter, L. L. (2016). Exposure to childhood trauma is associated with altered n-back activation and performance in healthy adults: implications for a commonly used working memory task. *Brain Imaging and Behavior*, *10*(1), 124–135. http://doi.org/10.1007/s11682-015-9373-9

Philip, N. S., Sweet, L. H., Tyrka, A. R., Price, L. H., Carpenter, L. L., Kuras, Y. I., … Niaura, R. S. (2013). Early life stress is associated with greater default network deactivation during working memory in healthy controls: a preliminary report. *Brain Imaging and Behavior*, *7*(2), 204–12. http://doi.org/10.1007/s11682-012-9216-x

Pineles, S. L., Shipherd, J. C., Mostoufi, S. M., Abramovitz, S. M., & Yovel, I. (2009). Attentional biases in PTSD: More evidence for interference. *Behaviour Research and Therapy*, *47*(12), 1050–1057. http://doi.org/10.1016/j.brat.2009.08.001

Pineles, S. L., Shipherd, J. C., Welch, L. P., & Yovel, I. (2007). The role of attentional biases in PTSD: Is it interference or facilitation? *Behaviour Research and Therapy*, *45*(8), 1903–1913. http://doi.org/10.1016/j.brat.2006.08.021

Polak, a R., Witteveen, A. B., Reitsma, J. B., & Olff, M. (2012). The role of executive function in posttraumatic stress disorder: a systematic review. *Journal of Affective Disorders*, *141*(1), 11–21. http://doi.org/10.1016/j.jad.2012.01.001

Pompei, F., Dima, D., Rubia, K., Kumari, V., & Frangou, S. (2011). Dissociable functional connectivity changes during the Stroop task relating to risk, resilience and disease expression in bipolar disorder. *NeuroImage*, *57*(2), 576–582. http://doi.org/10.1016/j.neuroimage.2011.04.055

Posner, M. I. (1980). Orienting of attention. *Quarterly Journal of Experimental Psychology*. http://doi.org/10.1080/00335558008248231

Posner, M. I. (2008). Measuring alertness. In *Annals of the New York Academy of Sciences* (Vol. 1129, pp. 193–199). http://doi.org/10.1196/annals.1417.011

Posner, M. I., & Petersen, S. E. (1990). The attention system of the human brain. *Annual Review of Neuroscience*, *13*, 25–42. http://doi.org/10.1146/annurev.ne.13.030190.000325

Power, J. D., Barnes, K., & Snyder, A. (2012). Spurious but systematic correlations in resting state functional connectivity MRI arise from head motion. *Neuroimage*, *59*(3), 2142–2154.

Power, J. D., Cohen, A. L., Nelson, S. M., Wig, G. S., Barnes, K. A., Church, J. A., … Petersen, S. E. (2011). Functional Network Organization of the Human Brain. *Neuron*, *72*(4), 665–678. http://doi.org/10.1016/j.neuron.2011.09.006

Power, J. D., & Petersen, S. E. (2013). Control-related systems in the human brain. *Current Opinion in Neurobiology*, *23*(2), 223–8. http://doi.org/10.1016/j.conb.2012.12.009

Prado, J., & Weissman, D. H. (2011). Spatial attention influences trial-by-trial relationships between response time and functional connectivity in the visual cortex. *NeuroImage*, *54*(1), 465–473. http://doi.org/10.1016/j.neuroimage.2010.08.038

Ptak, R. (2012). The Frontoparietal Attention Network of the Human Brain: Action, Saliency, and a Priority Map of the Environment. *The Neuroscientist*, *18*(5), 502–515. http://doi.org/10.1177/1073858411409051

Qureshi, S. U., Long, M. E., Bradshaw, M. R., Pyne, J. M., Magruder, K. M., Kimbrell, T., … Kunik, M. E. (2011). Does PTSD impair cognition beyond the effect of trauma? *The Journal of Neuropsychiatry and Clinical Neurosciences*, *23*(1), 16–28.

Rabinak, C. A., Angstadt, M., Welsh, R. C., Kenndy, A. E., Lyubkin, M., Martis, B., & Luan Phan, K. (2011). Altered amygdala resting-state functional connectivity in post-traumatic stress disorder. *Frontiers in Psychiatry*, *2*(62). http://doi.org/10.3389/fpsyt.2011.00062

Raichle, M. E. (2011). The restless brain. *Brain Connectivity*, *1*(1), 3–12. http://doi.org/10.1089/brain.2011.0019

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(2), 676–82. http://doi.org/10.1073/pnas.98.2.676

Raji, C. A., Willeumier, K., Taylor, D., Tarzwell, R., Newberg, A., Henderson, T. A., & Amen, D. G. (2015). Functional neuroimaging with default mode network regions distinguishes PTSD from TBI in a military veteran population. *Brain Imaging and Behavior*, *9*(3), 527–534. http://doi.org/10.1007/s11682-015-9385-5

Reineberg, A. E., Andrews-Hanna, J. R., Depue, B. E., Friedman, N. P., & Banich, M. T. (2015). Resting-state networks predict individual differences in common and specific aspects of executive function. *NeuroImage*, *104*, 69–78. http://doi.org/10.1016/j.neuroimage.2014.09.045

Resnick, H. S., Kilpatrick, D. G., Dansky, B. S., Saunders, B. E., & Best, C. L. (1993). Prevalence of civilian trauma and posttraumatic stress disorder in a representative national sample of women. *Journal of Consulting and Clinical Psychology*, *61*(6), 984–91.

Ressler, K. J., & Mayberg, H. S. (2007). Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. *Nature Neuroscience*, *10*(9), 1116–1124. http://doi.org/10.1038/nn1944

Rosenberg, M. D., Finn, E. S., Scheinost, D., Papademetris, X., Shen, X., Constable, R. T., & Chun, M. M. (2016). A neuromarker of sustained attention from whole-brain functional connectivity. *Nature Neuroscience*, *19*(1), 165–71. http://doi.org/10.1038/nn.4179

Rougemont-Bücking, A., Linnman, C., Zeffiro, T. A., Zeidan, M. A., Lebron-Milad, K., Rodriguez-Romaguera, J., … Milad, M. R. (2011). Altered processing of contextual information during fear extinction in PTSD: An fMRI study. *CNS Neuroscience and Therapeutics*, *17*(4), 227–236. http://doi.org/10.1111/j.1755-5949.2010.00152.x

Ruiz, S., Buyukturkoglu, K., Rana, M., Birbaumer, N., & Sitaram, R. (2014). Real-time fMRI brain computer interfaces: Self-regulation of single brain regions to networks. *Biological Psychology*. http://doi.org/10.1016/j.biopsycho.2013.04.010

Sadaghiani, S., & D'Esposito, M. (2014). Functional Characterization of the Cingulo-Opercular Network in the Maintenance of Tonic Alertness. *Cerebral Cortex (New York, N.Y. : 1991)*. http://doi.org/10.1093/cercor/bhu072

Samuelson, K. W., Neylan, T. C., Metzler, T. J., Lenoci, M., Rothlind, J., Henn-Haase, C., … Marmar, C. R. (2006). Neuropsychological functioning in posttraumatic stress disorder and alcohol abuse. *Neuropsychology*, *20*(6), 716–26. http://doi.org/10.1037/0894-4105.20.6.716

Satterthwaite, T. D., Wolf, D. H., Loughead, J., Ruparel, K., Elliott, M. A., Hakonarson, H., … Gur, R. E. (2012). Impact of in-scanner head motion on multiple measures of functional connectivity: Relevance for studies of neurodevelopment in youth. *NeuroImage*, *60*(1), 623–632. http://doi.org/10.1016/j.neuroimage.2011.12.063

Schafer, R. J., & Moore, T. (2007). Attention Governs Action in the Primate Frontal Eye Field. *Neuron*, *56*(3), 541–551. http://doi.org/10.1016/j.neuron.2007.09.029

Schweizer, K., & Moosebrugger, H. (2004). Attention and working memory as predictors of intelligence. *Intelligence*, *32*(4), 329–347. http://doi.org/10.1016/j.intell.2004.06.006

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., … Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *27*(9), 2349–2356. http://doi.org/10.1523/JNEUROSCI.5587-06.2007

Semple, W. E., Goyer, P. F., McCormick, R. A., ComptonToth, B., Morris, E., Donovana, B., … Donovan, B. S. (1996). Attention and regional cerebral blood flow in posttraumatic stress disorder patients with substance abuse histories. *Psychiatry Research: Neuroimaging*, *67*(1), 17–28. http://doi.org/http://dx.doi.org/10.1016/0925-4927(96)02735-7

Semple, W. E., Goyer, P. F., McCormick, R., Donovan, B., Muzic, R. F., Rugle, L., … Schulz, S. C. (2000). Higher brain blood flow at amygdala and lower frontal cortex blood flow in PTSD patients with comorbid cocaine and alcohol abuse compared with normals. *Psychiatry*, *63*(1), 65–74. http://doi.org/Article

Shallice, T. (1988). Specialisation within the semantic system. *Cognitive Neuropsychology*, *5*(1), 133–142. http://doi.org/10.1080/02643298808252929

Shanahan, M. A., Pennington, B. F., Yerys, B. E., Scott, A., Boada, R., Willcutt, E. G., … Defries, J. C. (2006). Processing Speed Deficits in Attention Deficit / Hyperactivity Disorder and Reading Disability. *Journal of Abnormal …*, *34*, 585–602. http://doi.org/10.1007/s10802-006-9037-8

Shapiro, S. L., Carlson, L. E., Astin, J. a., & Freedman, B. (2006). Mechanisms of mindfulness.

Journal of Clinical Psychology, *62*(3), 373–386. http://doi.org/10.1002/jclp

Sheehan, D. V, Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., … Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry*. http://doi.org/10.1016/S0924-9338(99)80239-9

Shin, L. M., Bush, G., Milad, M. R., Lasko, N. B., Brohawn, K. H., Hughes, K. C., … Pitman, R. K. (2011). Exaggerated activation of dorsal anterior cingulate cortex during cognitive interference: A monozygotic twin study of posttraumatic stress disorder. *American Journal of Psychiatry*, *168*(9), 979–985. http://doi.org/10.1176/appi.ajp.2011.09121812

Shin, L. M., Bush, G., Whalen, P. J., Handwerger, K., Cannistraro, P. a., Wright, C. I., … Rauch, S. L. (2007). Dorsal anterior cingulate function in posttraumatic stress disorder. *Journal of Traumatic Stress*, *20*(5), 701–712. http://doi.org/10.1002/jts.

Shirer, W. R., Ryali, S., Rykhlevskaia, E., Menon, V., & Greicius, M. D. (2012). Decoding subject-driven cognitive states with whole-brain connectivity patterns. *Cerebral Cortex*, *22*(1), 158–165. http://doi.org/10.1093/cercor/bhr099

Shucard, J. L., McCabe, D. C., & Szymanski, H. (2008). An event-related potential study of attention deficits in posttraumatic stress disorder during auditory and visual Go/NoGo continuous performance tasks. *Biological Psychology*, *79*(2), 223–33. http://doi.org/10.1016/j.biopsycho.2008.05.005

Simon, J. R., & Wolf, J. D. (1963). Choice reaction time as a function of angular stimulus-response correspondence and age. *Ergonomics*. http://doi.org/10.1080/00140136308930679

Smith, S. M., Fox, P. T., Miller, K. L., Glahn, D. C., Fox, P. M., Mackay, C. E., … Beckmann, C. F. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(31), 13040–5. http://doi.org/10.1073/pnas.0905267106

Sohlberg, M., & Mateer, C. (1989). *Introduction to cognitive rehabilitation: Theory and practice.* (M. M. Sohlberg & C. A. Mateer, Eds.). New York, NY, US: Guilford Press.

Solé-Padullés, C., Castro-Fornieles, J., de la Serna, E., Calvo, R., Baeza, I., Moya, J., … Sugranyes, G. (2016). Intrinsic connectivity networks from childhood to late adolescence: Effects of age and sex. *Developmental Cognitive Neuroscience*, *17*, 35–44. http://doi.org/10.1016/j.dcn.2015.11.004

Sripada, R. K., King, A. P., Garfinkel, S., Wang, X., Sripada, C., Welsh, R., & Liberzon, I. (2012). Altered resting-state amygdala functional connectivity in men with posttraumatic stress disorder. *Journal of Psychiatry & Neuroscience*, *37*(4), 241–249. http://doi.org/10.1503/jpn.110069

Sripada, R. K., King, A. P., Welsh, R. C., Garfinkel, S. N., Wang, X., Sripada, C. S., & Liberzon, I. (2012). Neural Dysregulation in Posttraumatic Stress Disorder: Evidence for Disrupted Equilibrium Between Salience and Default Mode Brain Networks. *Psychosomatic Medicine*, *74*(9), 904–11. http://doi.org/10.1097/PSY.0b013e318273bf33

Stein, M. B., Kennedy, C. M., & Twamley, E. W. (2002). Neuropsychological function in female

victims of intimate partner violence with and without posttraumatic stress disorder. *Biol Psychiatry*, *52*(11), 1079–1088. http://doi.org/S0006322302014142 [pii]

Steudte-Schmiedgen, S., Stalder, T., Kirschbaum, C., Weber, F., Hoyer, J., & Plessow, F. (2014). Trauma exposure is associated with increased context-dependent adjustments of cognitive control in patients with posttraumatic stress disorder and healthy controls. *Cognitive, Affective & Behavioral Neuroscience*, *14*(4), 1310–1319. http://doi.org/10.3758/s13415-014-0299-2

Stevens, A. A., Tappon, S. C., Garg, A., & Fair, D. A. (2012). Functional brain network modularity captures inter- and intra-individual variation in working memory capacity. *PLoS ONE*, *7*(1). http://doi.org/10.1371/journal.pone.0030468

Stevens, J. S., Ely, T. D., Sawamura, T., Guzman, D., Bradley, B., Ressler, K. J., & Jovanovic, T. (2016). Childhood Maltreatment Predicts Reduced Inhibition-Related Activity in the Rostral Anterior Cingulate in Ptsd, But Not Trauma-Exposed Controls. *Depression and Anxiety*, *33*(7), 614–622. http://doi.org/10.1002/da.22506

Storm, B. C., & White, H. a. (2010). ADHD and retrieval-induced forgetting: evidence for a deficit in the inhibitory control of memory. *Memory (Hove, England)*, *18*(3), 265–271. http://doi.org/10.1080/09658210903547884

Stroop, J. R. (1935). Stroop color word test. *J. Exp. Physiol.*, (18), 643–662. http://doi.org/10.1007/978-0-387-79948-3

Sumner, J. A., Hagan, K., Grodstein, F., Roberts, A. L., Harel, B., & Koenen, K. C. (2017). Posttraumatic stress disorder symptoms and cognitive function in a large cohort of middle-aged women. *Depression and Anxiety*, *34*(4), 356–366. http://doi.org/10.1002/da.22600

Sutker, P., Vasterling, J. J., Brailey, K., & Allain, A. N. (1995). Memory, attention, and executive deficits in POW survivors: Contributing biological and psychological factors. *Neuropsychology*, *9*(1), 118–125.

Sutker, P., Winstead, D. K., Galina, Z. H., & Allain, A. N. (1991). Cognitive deficits and psychopathology among former prisoners of war and combat veterans of the Korean conflict. *American Journal of Psychiatry*, *148*(1), 67–72. http://doi.org/10.1176/ajp.148.1.67

Sylvester, C., & Corbetta, M. (2012). Functional network dysfunction in anxiety and anxiety disorders. *Trends in …*, *35*(9), 527–535.

Szymanski, K., Sapanski, L., & Conway, F. (2011). Trauma and ADHD – Association or diagnostic confusion? A clinical perspective. *Journal of Infant, Child, and Adolescent Psychotherapy*, *10*(1), 51–59. http://doi.org/10.1080/15289168.2011.575704

Thiel, C. M., Zilles, K., & Fink, G. R. (2004). Cerebral correlates of alerting, orienting and reorienting of visuospatial attention: An event-related fMRI study. *NeuroImage*, *21*(1), 318–328. http://doi.org/10.1016/j.neuroimage.2003.08.044

Thomaes, K., Dorrepaal, E., Draijer, N., de Ruiter, M. B., Elzinga, B. M., van Balkom, A. J., … Veltman, D. J. (2012). Treatment effects on insular and anterior cingulate cortex activation during classic and emotional Stroop interference in child abuse-related complex post-

traumatic stress disorder. *Psychological Medicine*, *42*(11), 2337–2349. http://doi.org/10.1017/S0033291712000499

Thompson, K. G., Biscoe, K. L., & Sato, T. R. (2005). Neuronal basis of covert spatial attention in the frontal eye field. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *25*(41), 9479–9487. http://doi.org/10.1523/JNEUROSCI.0741-05.2005

Tomasi, D., Wang, R., Wang, G.-J., & Volkow, N. D. (2014). Functional Connectivity and Brain Activation: A Synergistic Approach. *Cerebral Cortex*, *24*(10), 2619–2629. http://doi.org/10.1093/cercor/bht119

Tursich, M., Ros, T., Frewen, P. A., Kluetsch, R. C., Calhoun, V. D., & Lanius, R. A. (2015). Distinct intrinsic network connectivity patterns of post-traumatic stress disorder symptom clusters. *Acta Psychiatrica Scandinavica*, *132*(1), 29–38. http://doi.org/10.1111/acps.12387

Twamley, E. W., Hami, S., & Stein, M. B. (2004). Neuropsychological function in college students with and without posttraumatic stress disorder. *Psychiatry Research*, *126*(3), 265–74. http://doi.org/10.1016/j.psychres.2004.01.008

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., … Joliot, M. (2002). Automated Anatomical Labeling of Activations in SPM Using a Macroscopic Anatomical Parcellation of the MNI MRI Single-Subject Brain. *Neuroimage*, *15*(1), 273–289.

Uddin, L. Q., Kelly, a. M. C., Biswal, B. B., Castellanos, F. X., & Milham, M. P. (2009). Functional Connectivity of Default Mode Network Components: Correlation, Anticorrelation, and Causality. *Human Brain Mapping*, *30*(2), 625–637. http://doi.org/10.1002/hbm.20531

Uddo, M., Vasterling, J., Brailey, K., & Sutker, P. (1993). Memory and attention in combat-related post-traumatic stress disorder (PTSD). *Journal of Psychopathology …*, *15*(1), 43–52.

van den Heuvel, M. P., Stam, C. J., Kahn, R. S., & Hulshoff Pol, H. E. (2009). Efficiency of functional brain networks and intellectual performance. *The Journal of Neuroscience*, *29*(23), 7619–24. http://doi.org/10.1523/JNEUROSCI.1443-09.2009

van Donkelaar, P., Langan, J., Rodriguez, E., Drew, A., Halterman, C., Osternig, L. R., … Chou, L. (2005). Attentional deficits in concussion. *Brain Injury*, *19*(12), 1031–1039. http://doi.org/10.1080/02699050500110363

van Rooij, S. J. H., Geuze, E., Kennis, M., Rademaker, A. R., & Vink, M. (2014). Neural Correlates of Inhibition and Contextual Cue Processing Related to Treatment Response in PTSD. *Neuropsychopharmacology*, *40*(10). http://doi.org/10.1038/npp.2014.220

VanElzakker, M. B. (2016). The origin of concentration problems in posttraumatic stress disorder. *Dissertation Abstracts International: Section B: The Sciences and Engineering*, *76*(10–B(E)).

Vasterling, J. J., Brailey, K., Constans, J., & Sutker, P. (1998). Attention and memory dysfunction in posttraumatic stress disorder. *Neuropsychology*, *12*(1), 125–133.

Vasterling, J. J., Duke, L. M., Brailey, K., Constans, J. I., Allain, A. N., & Sutker, P. (2002). Attention, learning, and memory performances and intellectual resources in Vietnam

veterans: PTSD and no disorder comparisons. *Neuropsychology*, *16*(1), 5–14. http://doi.org/10.1037//0894-4105.16.1.5

Vinogradov, S., Fisher, M., & de Villers-Sidani, E. (2012). Cognitive training for impaired neural systems in neuropsychiatric illness. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *37*(1), 43–76. http://doi.org/10.1038/npp.2011.251

Visintin, E., De Panfilis, C., Antonucci, C., Capecci, C., Marchesi, C., & Sambataro, F. (2015). Parsing the intrinsic networks underlying attention: A resting state study. *Behavioural Brain Research*, *278*, 315–322. http://doi.org/10.1016/j.bbr.2014.10.002

Vossel, S., Geng, J. J., & Fink, G. R. (2014). Dorsal and ventral attention systems: distinct neural circuits but collaborative roles. *The Neuroscientist : A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, *20*(2), 150–9. http://doi.org/10.1177/1073858413494269

Vossel, S., Thiel, C. M., & Fink, G. R. (2006). Cue validity modulates the neural correlates of covert endogenous orienting of attention in parietal and frontal cortex. *NeuroImage*, *32*(3), 1257–64. http://doi.org/10.1016/j.neuroimage.2006.05.019

Vossel, S., Weidner, R., Driver, J., Friston, K. J., & Fink, G. R. (2012). Deconstructing the architecture of dorsal and ventral attention systems with dynamic causal modeling. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *32*(31), 10637–48. http://doi.org/10.1523/JNEUROSCI.0414-12.2012

Voytko, M. L., Olton, D. S., Richardson, R. T., Gorman, L. K., Tobin, J. R., & Price, D. L. (1994). Basal forebrain lesions in monkeys disrupt attention but not learning and memory. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *14*(1), 167–86. http://doi.org/http://www.jneurosci.org/content/15/11/7315

Weathers, F. W., Bovin, M. J., Lee, D. J., Sloan, D. M., Schnurr, P. P., Kaloupek, D. G., … Marx, B. P. (2017). The Clinician-Administered PTSD Scale for DSM–5 (CAPS-5): Development and Initial Psychometric Evaluation in Military Veterans. *Psychological Assessment*. http://doi.org/10.1037/pas0000486

Wechsler, D. (2008). *Wechsler adult intelligence scale–Fourth Edition (WAIS–IV). San Antonio*. Texas: NCS Pearson.

Wechsler, D. (2009). *Wechsler Memory Scale-(WMS-IV). New York: The Psychological Corporation*. New York, NY, US: The Psychological Corporation. http://doi.org/10.1037/t15175-000

Weierich, M. R., Treat, T. a., & Hollingworth, A. (2008). *Theories and measurement of visual attentional processing in anxiety*. *Cognition & Emotion* (Vol. 22). http://doi.org/10.1080/02699930701597601

Weinbach, N., Henik, A., Shofty, I., Gabay, S., & Henik, A. (2013). The Relationship Between Alertness and Executive Control. *Cognition*, *38*(3), 454–458. http://doi.org/10.3758/s13414-013-0501-6

Weissman-Fogel, I., Moayedi, M., Taylor, K. S., Pope, G., & Davis, K. D. (2010). Cognitive and

default-mode resting state networks: Do male and female brains "rest" differently? *Human Brain Mapping*, *31*(11), 1713–1726. http://doi.org/10.1002/hbm.20968

Weissman, D. H. (2004). The Neural Mechanisms for Minimizing Cross-Modal Distraction. *Journal of Neuroscience*, *24*(48), 10941–10949. http://doi.org/10.1523/JNEUROSCI.3669-04.2004

Weissman, D. H., Roberts, K. C., Visscher, K. M., & Woldorff, M. G. (2006). The neural bases of momentary lapses in attention. *Nature Neuroscience*, *9*(7), 971–978. http://doi.org/10.1038/nn1727

Westlye, L. T., Grydeland, H., Walhovd, K. B., & Fjell, A. M. (2011). Associations between regional cortical thickness and attentional networks as measured by the attention network test. *Cerebral Cortex*, *21*(2), 345–356. http://doi.org/10.1093/cercor/bhq101

Winship, C., & Korenman, S. (1997). Does staying in school make you smarter? The effect of education on IQ in The Bell Curve. In *Intelligence, Genes, and Success: Scientists Respond to The Bell Curve* (pp. 215–234). New York: Springer. http://doi.org/10.1007/978-1-4612-0669-9_10

Winstanley, C. A., Eagle, D. M., & Robbins, T. W. (2006). Behavioral models of impulsivity in relation to ADHD: translation between clinical and preclinical studies. *Clinical Psychology Review*, *26*(4), 379–95. http://doi.org/10.1016/j.cpr.2006.01.001

Wu, J., Ge, Y., Shi, Z., Duan, X., Wang, L., Sun, X., & Zhang, K. (2010). Response inhibition in adolescent earthquake survivors with and without posttraumatic stress disorder: a combined behavioral and ERP study. *Neuroscience Letters*, *486*(3), 117–21. http://doi.org/10.1016/j.neulet.2010.07.040

Wu, R.-Z., Zhang, J.-R., Qiu, C.-J., Meng, Y.-J., Zhu, H.-R., Gong, Q.-Y., … Zhang, W. (2011). Study on resting-state default mode network in patients with posttraumatic stress disorder after the earthquake. *Sichuan Da Xue Xue Bao. Yi Xue Ban = Journal of Sichuan University. Medical Science Edition*, *42*(3), 397–400.

Xuan, B., Mackie, M. A., Spagna, A., Wu, T., Tian, Y., Hof, P. R., & Fan, J. (2016). The activation of interactive attentional networks. *NeuroImage*, *129*, 308–319. http://doi.org/10.1016/j.neuroimage.2016.01.017

Yehuda, R., Golier, J. A., Halligan, S. L., & Harvey, P. D. (2004). Learning and memory in Holocaust survivors with posttraumatic stress disorder. *Biological Psychiatry*, *55*(3), 291–295. http://doi.org/10.1016/S0006-3223(03)00641-3

Yennu, A., Tian, F., Smith-Osborne, A., J Gatchel, R., Woon, F. L., & Liu, H. (2016). Prefrontal responses to Stroop tasks in subjects with post-traumatic stress disorder assessed by functional near infrared spectroscopy. *Scientific Reports*, *6*, 30157. http://doi.org/10.1038/srep30157

Yeo, B. T. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., … Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, *106*(3), 1125–65. http://doi.org/10.1152/jn.00338.2011

Yin, Y., Jin, C., Eyler, L., Jin, H., Hu, X., & Duan, L. (2012). Altered regional homogeneity in post-traumatic stress disorder: a resting-state functional magnetic resonance imaging study. *Neuroscience …*, *28*(5), 541–549.

Zalewski, C., Thompson, W., & Gottesman, I. (1994). Comparison of Neuropsychological Test Performance in PTSD, Generalized Anxiety Disorder, and Control Vietnam Veterans. *Assessment*. http://doi.org/10.1177/1073191194001002003

Zhang, Y., Liu, F., Chen, H., Li, M., Duan, X., Xie, B., & Chen, H. (2015). Intranetwork and internetwork functional connectivity alterations in post-traumatic stress disorder. *Journal of Affective Disorders*, *187*, 114–121. http://doi.org/10.1016/j.jad.2015.08.043

Zhang, Y., Xie, B., Chen, H., Li, M., Liu, F., & Chen, H. (2016). Abnormal Functional Connectivity Density in Post-traumatic Stress Disorder. *Brain Topography*, *29*(3), 405–411. http://doi.org/10.1007/s10548-016-0472-8

Zhou, Y., Wang, Z., Qin, L., Wan, J., Sun, Y., Su, S., … Berman, M. (2012). Early altered resting-state functional connectivity predicts the severity of post-traumatic stress disorder symptoms in acutely traumatized subjects. *PloS One*, *7*(10), e46833. http://doi.org/10.1371/journal.pone.0046833

Zou, Q., Ross, T. J., Gu, H., Geng, X., Zuo, X.-N., Hong, L. E., … Yang, Y. (2013). Intrinsic resting-state activity predicts working memory brain activation and behavioral performance. *Human Brain Mapping*, *34*(12), 3204–15. http://doi.org/10.1002/hbm.22136

Zuo, X. N., Kelly, C., Adelstein, J. S., Klein, D. F., Castellanos, F. X., & Milham, M. P. (2010). Reliable intrinsic connectivity networks: test-restest evaluation using ICA and dual regression approach. *Neuroimage*, *49*(3), 2163–2177.