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Cue-dependent inhibition in posttraumatic stress disorder and attention-deficit/hyperactivity disorder

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ABSTRACT

Objective: Attention-deficit/hyperactivity disorder (ADHD) and posttraumatic stress disorder (PTSD) are common among military veterans, but the comorbidity of these two psychiatric disorders remains largely understudied. Evaluating response inhibition and cue-dependent learning as behavioral and neurocognitive mechanisms underlying ADHD/PTSD can inform etiological models and development of tailored interventions.

Method: A cued go/no-go task evaluated response inhibition in 160 adult males. Participants were recruited from the community and a Veterans Administration medical center. Four diagnostic groups were identified: ADHD-only, PTSD-only, ADHD + PTSD, controls.

Results: Group differences were observed across most indices of inhibitory functioning, reaction time, and reaction time variability, whereby PTSD-only and ADHD + PTSD participants demonstrated deficits relative to controls. No cue dependency effects were observed.

Conclusion: Finding complement prior work on neurocognitive mechanisms underlying ADHD, PTSD, and ADHD + PTSD. Lack of expected group differences for the ADHD-only group may be due to limited power. Additional work is needed to better characterize distinctions among clinical groups, as well as to test effects among women and youth.

1. Introduction

Post-traumatic stress disorder (PTSD) is a commonly occurring and debilitating condition following exposure to life-threatening events (e.g., physical assault, sexual assault, combat exposure). Epidemiological studies suggest that even though the vast majority of US citizens experience a traumatic event in their lifetime (Breslau, 2009), the 12-month prevalence of PTSD in US adults is only 3.5%. However, this rate is substantially higher among veterans. For example, 48.5% of Operation Enduring Freedom (OEF) or Operation Iraqi Freedom (OIF) soldiers screened positive for PTSD symptoms (Khaylis, Polusny, Erbes, Gewitz, & Rath, 2011). Further, 46% of active duty or retired OEF/OIF soldiers met diagnostic criteria for PTSD (Pittman, Goldsmith, Lemmer, Kilmer, & Baker, 2012). In addition to the high rates of PTSD in veterans, lifetime comorbidity of PTSD with any psychiatric disorder (e.g., depression, substance use disorders, anxiety disorders) has been found to be as high as 88%.

Attention-deficit/hyperactivity disorder (ADHD) has also been shown to commonly occur among military personnel with estimates at approximately 10% (Antshel et al., 2013; Hanson et al., 2012), whereas estimates of adult ADHD in the general population range from 1.6–4.4% (Kessler et al., 2006; Simon, Czobar, Bálint, & Mészáros Bitter, 2009). ADHD is estimated to co-occur with PTSD at rates ranging from of 12–28% in veterans (Adler, Kunz, Chua, Rotrosen, & Resnik, 2004; Harrington et al., 2012). Rates of PTSD among adults with ADHD were six times higher than among adults without ADHD (Antshel et al., 2013). Furthermore, research has demonstrated that ADHD symptom severity significantly predicts PTSD symptom severity (Harrington et al., 2012).

Though research has begun to uncover the increased risk for PTSD among individuals with ADHD, less is known about the mechanisms by which these two disorders co-occur. Neurocognitive performance represents one potential area that may help to explain ADHD-PTSD comorbidity. Given that both ADHD and PTSD literatures individually identify deficits in neurocognitive performance (Barkley, 1997; Bremner, 1999; Buckley, Blanchard, & Neill, 2000), investigating

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specific facets of neurocognitive functioning signifies a promising line of research. Understanding neurocognitive performance among people with PTSD, ADHD, comorbid ADHD-PTSD, and healthy controls will help in building more sophisticated etiological models of the disorders, and help guide targeted treatments that address underlying deficits.

One aspect of neurocognition that has been routinely explored in individuals with ADHD is response inhibition or the inhibition of prepotent or ongoing responses (Barkley, 1997; Oosterlan, Logan, & Sergeant, 1998). This deficit in response inhibition and interference control has been suggested as a basis for the core features of ADHD (Barkley, 1997). Response inhibition has been routinely measured using the "Go/No Go" Task in which there are two stimuli, a "go" and a "no-go." Participants are then instructed to press a button, as quickly as possible, when a "go" stimulus is presented and to inhibit this response when a "no-go" stimulus is presented (Simmonds, Pekar, & Mostofsky, 2008). Research suggests adults with ADHD show lower accuracy rates, increased commission errors, increased response interference, and a decreased likelihood to consciously detect these errors (Morein-Zamir et al., 2014; O'Connell et al., 2009; Sebastian et al., 2012; Woltering, Liu, Rokeach, & Tannock, 2013).

Response inhibition also has been investigated, albeit to a lesser degree, within the PTSD literature. According to the DSM-5, PTSD is comprised of four clusters of symptoms: re-experiencing symptoms, avoidance, negative cognitions/mood, and arousal (American Psychiatric Association, 2013). Kertzman, Avital, Weizman, and Segal, 2014 pointed to re-experiencing symptoms as well as sensory stimuli leading to cognitive deficits such as response inhibition in patients with PTSD. Self-reported behavioral inhibition is significantly related to PTSD symptoms, especially PTSD symptoms in the avoidance cluster among veterans (Myers, VanMeenen, & Servatius, 2012). Research using the Go/No-Go task has demonstrated that veterans with PTSD show a decreased inhibitory response and greater false-alarm rate (Tillman et al., 2010) as well as a significantly more variable reaction times (Swick, Honzel, Larsen, & Ashley, 2013) when compared to veterans without PTSD. Several studies have investigated behavioral and neural processing deficits in both inhibitory functioning and evaluation of contextual cues in veterans and civilians with PTSD, in line with evidence that problems in inhibiting a fear response and interpreting environmental safety vs. danger information may underlie symptoms of the disorder (Falconer et al., 2012; Jovanovic, Kazama, Bachevalier, & Davis, 2012; Jovanovic et al., 2013; Van Rooij, Geuze, Kennis, Rademaker, & Vink., 2015). Results from those studies suggest that behavioral and neural deficits in inhibition and contextual cue processing may extend beyond fear responses in PTSD and may be more generalized, core deficits of the disorder (Jovanovic et al., 2012, 2013; Van Rooij et al., 2014, 2015). Although some of the studies evaluated the potential effects of comorbid psychiatric conditions (e.g., mood disorders), none directly reported on the potential influence of ADHD on observed group differences.

Little is known about the inhibitory functioning among individuals with ADHD and comorbid PTSD. To our knowledge there have been no studies that have looked at response inhibition in groups of veterans and civilians with ADHD, PTSD, and comorbid ADHD-PTSD compared to veterans and civilians without a history of psychopathology. It is unknown whether people with comorbid ADHD-PTSD have worse inhibitory functioning than people with either disorder alone.

When evaluating inhibitory responses, it is important to consider the potential influence of environmental factors, such as cues that may guide response preparation. Given the symptoms seen in PTSD, especially those related to arousal and hypervigilance (American Psychiatric Association, 2013), veterans with PTSD may be especially attuned to environmental cues to inform behavioral control (e.g., vigilance for danger cues). Some evidence suggests that valid cues can aid in the anticipation of an appropriate response against inhibitory impairment. For example, in alcohol use literature, antecedent cues during the Go/No-Go task can help dampen inhibitory deficits when individuals are under the influence of alcohol (Marczinski & Fillore, 2005). However, the use of antecedent cues during the Go/No-Go task has not been shown to significantly improve response inhibition deficits in adults with ADHD (Roberts, Milich, & Fillmore, 2016). It is unknown whether having a diagnosis of PTSD would influence cue dependency among veterans and community adults with and without comorbid ADHD.

The current study seeks to investigate how response inhibition is influenced by diagnoses of ADHD, PTSD, or comorbid ADHD-PTSD in veterans and civilians compared to healthy controls. Furthermore, the study will examine how antecedent cues effect response inhibition in these groups. We predicted that participants with ADHD – with and without PTSD – would demonstrate inhibitory deficits relative to controls. We also hypothesized that participants with PTSD would demonstrate greater cue dependency than participants without PTSD.

2. Method

2.1. Participants

Participants in this study were 160 men (mean age = 30.8 years, SD = 7.6; 75.2% white/Caucasian; 14.9% black/African-American; 3.0% biracial; 3.1% Hispanic). Participants were either recruited from the local community or through a large Veterans Administration (VA) Medical Center in the southeastern U.S. Participants enrolled from the VA were combat veterans of Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) missions. Of enrolled participants, 17 met criteria for ADHD only (47% veterans), 25 met criteria for PTSD only (100% veterans), 26 met criteria for ADHD + PTSD (100% veterans), and 93 participants met criteria for neither ADHD nor PTSD (23% veterans). Basic demographic characteristics for each group are summarized in Table 1.

2.1.1. Inclusion and exclusion criteria

To be eligible for this study, participating veterans were required to have a history of combat exposure, as evidenced by formal release or discharge paperwork (i.e., DD Form 214), a report of combat exposure during the interview with a psychiatrist (ZW, MH, FS), and a minimum score of 10 on the Combat Exposure Scale (CES) (Lund, Foy, Sipprelle, & Strachan, 1984). Participants were not required to meet diagnostic criteria for PTSD or ADHD to enroll, and participants with major depression, and anxiety disorders were included. Subjects with other Axis I psychiatric disorders were excluded from this study; this included current or lifetime DSM-IV schizophrenia, other psychotic disorders, bipolar disorder, and active substance abuse or dependence in the past six months. Individuals with a past history of substance abuse and dependence were included if the last use of the substance was over 6 months prior to the enrollment. There were no inclusion or exclusion criteria based on sociodemographic characteristics.

2.2. Procedure

The study protocol was approved by the Institutional Review Board (IRB) of the academic institution where this research was conducted. A brief description of the study, including explanation of the voluntary nature of participation, was given to potential participants by a trained research assistant. People who expressed interest in participation were screened to determine eligibility for study involvement using the inclusion and exclusion criteria described below. Institutionally approved informed consent was obtained from all participants before the protocol began.

After collecting demographic and deployment information, participants were assessed by a trained research assistant for the presence of psychiatric disorders with the *Mini-International Neuropsychiatric Interview* (MINI) (Lecrubier et al., 1997). PTSD symptoms were assessed with the Clinician Administered PTSD Scale (CAPS) (Blake et al., 1995), and ADHD symptoms were assessed with the Conners Adult ADHD