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Executive function in posttraumatic stress disorder (PTSD) and the influence of comorbid depression

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ABSTRACT

Background: Posttraumatic stress disorder (PTSD) has been associated with neurocognitive deficits, such as impaired verbal memory and executive functioning. Less is known about executive function and the role of comorbid depression in PTSD. Recently, studies have shown that verbal memory impairments may be associated with comorbid depressive symptoms, but their role in executive function impairments is still unclear.
Objective: To examine several domains of executive functioning in PTSD and the potentially mediating role of comorbid depressive symptoms in the relationship between executive function and PTSD.
Method: Executive functioning was assessed in 28 PTSD patients and 28 matched trauma-exposed controls. The Cambridge Neuropsychological Test Automated Battery (CANTAB) with subtests measuring response inhibition (SST), flexibility/set shifting (IED), planning/working memory (OTS) and spatial working memory (SWM) was administered in PTSD patients and trauma-exposed controls. Regression analyses were used to assess the predictive factor of PTSD symptoms (CAPS) and depressive symptoms (HADS-D) in relation to executive function when taking into account the type of trauma. Pearson's correlations were used to examine the association between PTSD symptom clusters (CAPS) and executive function. The mediating effects of depression and PTSD were assessed using regression coefficients and the Sobel's test for mediation.
Results: Our findings indicate that PTSD patients performed significantly worse on executive function than trauma-exposed controls in all domains assessed. PTSD symptoms contributed to executive functioning impairments (SST median correct, IED total errors, OTS latency to correct, SWM total errors and SWM strategy). Adding depressive symptoms to the model attenuated these effects. PTSD symptom clusters 'numbing' and to a lesser extent 'avoidance' were more frequently associated with worse executive function (i.e., IED total errors, OTS latency to correct and SWM total errors) than 'reexperiencing' and 'hyperarousal'. Depressive symptoms mediated the relation between PTSD and executive function on some executive function measures (IED total errors and OTS latency to correct), whereas PTSD did not mediate the relation between depression and executive function.
Conclusions: PTSD patients perform worse on executive function. The impairments seem to be mostly associated with the less specific PTSD symptom cluster of 'numbing'. Depressive symptoms seem to mediate the relationship between PTSD and executive function. These findings may have clinical implications with regard to treatment indication and prognosis.

1. Background

Posttraumatic stress disorder (PTSD) has increasingly been associated with impairments in neurocognitive domains such as verbal memory (Johnsen & Asbjornsen, 2008) and executive functioning (Samuelson et al., 2006; Stein, Kennedy, & Twamley, 2002; Polak, Witteveen, Reitsma, & Olff, 2012).

The widely adopted model on neurocircuitry of PTSD suggests a hyperactive amygdala and hypoactivation of the medial prefrontal cortex (Patel, Spreng, Shin, & Girard, 2012; Quide, Witteveen, El-Hage, Veltman, & Olff, 2012). A structural finding that was repeatedly found among PTSD patients was hippocampal volume reduction (Hull, 2002). Consistent with the involvement

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of frontal areas, several studies have shown impairment in differential domains of executive functioning in PTSD, such as attention and working memory (El-Hage, Quidé, Radua, & Olff, 2013; Gilbertson, Gurvits, Lasko, Orr, & Pitman, 2001; Jenkins, Langlais, Delis, & Cohen, 2000; Meewisse et al., 2005; Samuelson et al., 2006), inhibitory functions (Jenkins et al., 2000; Koso & Hansen, 2006; Leskin & White, 2007) and flexibility and planning (Beckham, Crawford, & Feldman, 1998; Jenkins et al., 2000; Stein et al., 2002). Although impairment in executive functioning was not consistently found over studies (Crowell, Kieffer, Siders, & Vanderploeg, 2002; Twamley, Hami, & Stein, 2004; Zalewski, Thompson, & Gottesman, 1994), a recent review and meta-analysis indicated an overall dysfunction in executive functioning in PTSD when compared to trauma-exposed and healthy controls (Polak, Witteveen, Visser, et al., 2012). PTSD symptoms could directly lead to deficits in executive functioning; reexperiencing, sleeping problems, problems with concentration or hyperarousal may interrupt with working memory performance and inhibitory functions (Vasterling et al., 2002). Another possibility is that subtle impairments may predate PTSD, and that impaired executive function, and especially difficulty inhibiting stimuli, and difficulty disengaging from threatening stimuli may lead to developing PTSD symptoms such as reexperiencing and hyperarousal symptoms after trauma exposure (Aupperle, Melrose, Stein, & Paulus, 2012). The authors imply that difficulty inhibiting may consequently result in other coping strategies such as avoidance in order to be able to decrease reexperiencing and hyperarousal symptoms.

Although several studies have focused on executive function impairment in PTSD, there is less knowledge on the exact causal pathway of this relationship. Results of other studies indicate that verbal memory impairments in PTSD are associated with comorbid depressive symptoms (Burris, Ayers, Ginsberg, & Powell, 2008; Johnsen, Kanagaratnam, & Asbjornsen, 2008). Likewise, executive dysfunction in PTSD patients may be associated with comorbid depression. Previously, major depressive disorder without any psychiatric comorbidity showed to be associated with executive function impairments (Austin, Mitchell, & Goodwin, 2001; Elliott et al., 1996; Gohier et al., 2009). These impairments could be explained by several factors, such as reduced motivation, abnormal catastrophic responses to negative feedback and attentional biases, i.e., difficulty with inhibiting interfering irrelevant negative material (Porter, Bourke, & Gallagher, 2007). It is possible that comorbid depression in PTSD may also influence the relation between PTSD and executive function and (partly) mediate the relationship of PTSD and executive function. Recent studies point towards that possibility, i.e., a meta-analysis of (Polak, Witteveen, Visser, et al., 2012) found an effect of depressive symptoms on executive function tests. Furthermore, a study with a sample of veteran participants with PTSD indicated that self-reported anxiety and depressive symptoms mediate the relation of PTSD and working memory impairments (Dretsch et al., 2012). The authors of this study only focused on one domain of executive function, namely working memory, and suggested that comorbid depressive symptoms may mediate the relation between PTSD and executive function though were unable to determine the interrelationship between PTSD and depression in detail. Currently, the exact relation between PTSD, comorbid depression and executive function is still uncertain. This prompted us to look more closely at executive function and the association between PTSD, its symptom clusters ('reexperiencing', 'avoidance' and 'numbing' and 'hyperarousal'), and executive function and to explore whether comorbid depression mediates the relationship between PTSD and executive function or whether PTSD is a (partial) mediating variable of an actual relationship between depression and executive function.

In the current study the performance in several domains of executive functioning (i.e., response inhibition, flexibility and set shifting, planning and working memory) in PTSD patients is compared with trauma-exposed controls. Also, the role of comorbid depressive symptoms is examined, i.e., the association of PTSD symptom clusters and executive function as well as the mediating role of depression in the relationship between executive function and PTSD. We hypothesize that PTSD patients perform worse on all domains of executive function measures in comparison with controls, as this is in line with previous data (Polak, Witteveen, Visser, et al., 2012; Koso & Hansen, 2006; Samuelson et al., 2006; Stein et al., 2002). Secondly, we expect that depression has a prominent role in executive dysfunction and in relation to that, we expect to find that 'numbing' in particular is associated with executive dysfunction, as these symptoms are closely related to depression (i.e., disinterest in activities and numbing). Furthermore, we hypothesize that depressive symptoms partly mediate the relation between PTSD and executive function.

2. Method

2.1. Participants

PTSD patients were recruited from the outdoor clinic of the Academic Medical Center (AMC) in Amsterdam, the Netherlands and were enrolled in a currently ongoing randomized controlled trial (Polak, Witteveen, Visser, et al., 2012).

The initial PTSD sample comprised of 47 patients. Inclusion criteria for PTSD patients were: age between 18 and 65 years and primary diagnosis of PTSD according to the DSM-IV criteria. Severe comorbid depressive disorder was an exclusion criterion as well as comorbid schizophrenia, bipolar disorder or depression with psychotic features or substance dependence or abuse. Nineteen patients were excluded based on the following criteria: presence of comorbid axis II disorders ($n = 4$), presence of excessive substance or alcohol use over the past two months ($n = 1$), current use of psychotropic medication ($n = 7$), a neurological disorder ($n = 1$), previous loss of consciousness of more than 30 min ($n = 1$), a serious medical condition ($n = 1$), not meeting all PTSD symptoms according to the DSM-IV criteria at time of the measurement ($n = 3$), and no informed consent present ($n = 1$). After these exclusions, 28 PTSD patients remained for the analysis. Of the included patients, 13 patients had a comorbid depressive disorder and 15 patients did not have a depressive disorder, according to the DSM-IV criteria. Furthermore, two patients were diagnosed with a comorbid pain disorder and one patient with a comorbid specific phobia. Psychopathology was assessed with the M.I.N.I.-Plus.

Trauma-exposed controls were matched with the PTSD group according to gender, age and years of education. The initial sample comprised of 43 controls. Controls with any current psychiatric disorder as measured with the M.I.N.I.-Plus were excluded, including anxiety disorders, depressive disorder, schizophrenia, bipolar disorder and substance dependence or abuse. Fifteen controls were excluded based on the following criteria: substance (alcohol or drugs) dependence or abuse ($n = 6$) or current psychotropic medication ($n = 1$). Controls with a history of a diagnosis of PTSD ($n = 3$) were also excluded. Some trauma-exposed controls were excluded due to neurological disorders ($n = 1$) or loss of consciousness of more than 30 min ($n = 4$). The final sample after exclusions consisted of 28 trauma-exposed controls.

2.2. Procedures

Patients were seen at the outpatient clinic by psychiatrists and psychologists in order to assess axis I and axis II DSM-IV diagnoses which was confirmed using the M.I.N.I.-Plus (Sheehan et al., 1998).

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