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Functional network topology associated with posttraumatic stress disorder in veterans

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ABSTRACT

Posttraumatic stress disorder (PTSD) is a disabling disorder associated with resting state functional connectivity alterations. However, whether specific brain regions are altered in PTSD or whether the whole brain network organization differs remains unclear. PTSD can be treated with trauma-focused therapy, although only half of the patients recover after treatment. In order to better understand PTSD psychopathology our aim was to study resting state networks in PTSD before and after treatment. Resting state functional magnetic resonance images were obtained from veterans with PTSD (n = 50) and controls (combat and civilian controls; n = 54) to explore which network topology properties (degree and clustering coefficient) of which brain regions are associated with PTSD. Then, PTSD-associated brain regions were investigated before and after treatment. PTSD patients were subdivided in persistent (n = 22) and remitted PTSD patients (n = 17), and compared with combat controls (n = 22), who were also reassessed. Prior to treatment associations with PTSD were found for the degree of orbitofrontal, and temporoparietal brain regions, and for the clustering coefficient of the anterior cingulate cortex. No significant effects were found over the course of treatment. Our results are in line with previous resting state studies, showing resting state connectivity alterations in the salience network and default mode network in PTSD, and also highlight the importance of other brain regions. However, network metrics do not seem to change over the course of treatment. This study contributes to a better understanding of the psychopathology of PTSD.

1. Introduction

Posttraumatic stress disorder (PTSD) is a trauma- and stressor-related disorder that can develop after experiencing a traumatic event (American Psychiatric Association, 2013). Since many veterans are exposed to traumatic events during deployment, they are at risk for developing PTSD. About six to twelve percent of the veterans who have been deployed to Afghanistan and Iraq develop a high level of PTSD symptoms (Hoge et al., 2004; Reijnen et al., 2014). Trauma-focused therapy is shown to be an effective therapeutic strategy for PTSD, which stimulates fear habituation and induces fear extinction of trauma-related memories (Rothbaum and Davis, 2003). However, only half of the PTSD patients recover after trauma-focused therapy (Bradley et al., 2005). In order to improve response rates it is important to understand the psychopathology of PTSD, and to determine biological markers for treatment outcome. Therefore, we investigated neurobiological alterations in PTSD and controls in a longitudinal design, before and after trauma-focused therapy.

PTSD has been associated with hyperactivity of limbic brain regions, such as the amygdala, and hypo-activity of brain areas involved in emotional regulation, such as the ventromedial prefrontal cortex (vmPFC; (Liberzon and Sripada, 2007; Rauch et al., 2006). Over the last decade alterations in resting state functional connectivity have been reported in PTSD in cross-sectional studies. Resting state functional connectivity refers to a correlation between brain activation of different regions, indicating synchronization of neural activation of those regions during rest (Greicius et al., 2009). It has been suggested that alterations in two specific networks may underlie PTSD: the default mode network (DMN), and the salience network (SN; Daniels et al., 2010; Sripada et al., 2012b). The DMN is a network that is activated during rest, and consists of the medial prefrontal cortex, posterior cingulate cortex, precuneus and temporoparietal regions (Greicius et al., 2009; Raichle et al., 2001). The DMN is thought to be involved in autobiographical memory processes and self-referential processing (Kelley et al., 2002). The SN, including the dorsal anterior cingulate cortex (ACC) and insula as core nodes, has been associated with attentional processes (Seeley

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et al., 2007). Alterations in the DMN and SN have been reported during resting state in PTSD compared to non-trauma-exposed controls (Bluhm et al., 2009; Daniels et al., 2010), and trauma-exposed controls (Sripada et al., 2012b). However, alterations in functional connectivity between other regions are also found compared to non-trauma-exposed controls (Chen and Etkin, 2013; Kennis et al., 2014), and to trauma-exposed controls (Brown et al., 2014; Dunkley et al., 2014; Sripada et al., 2012a; Yin et al., 2011). Therefore, it remains unclear whether resting state functional connectivity is altered in the DMN and SN only in PTSD, or whether the whole brain network is altered. Moreover, it has been suggested that normalization of resting state network connectivity may be related to a reduction in (specific) PTSD symptoms (Lanius et al., 2015). For example, changes in arousal level may be related to alterations in a network including the insula and dorsal anterior cingulate cortex (ACC), and an altered sense of self can be related to alterations in a network including the medial PFC and posterior cingulate cortex (PCC; Tursich et al., 2015). However, the effect of treatment on resting state functional connectivity has not been investigated. Therefore, it is relevant to study which brain regions are in particular altered in PTSD, and if treatment effects functional connectivity of these regions.

Recently, functional magnetic resonance imaging (fMRI) studies have emerged investigating neurobiological effects of treatment in PTSD. Task-based activation studies reported pre-treatment differences in the prefrontal cortex, anterior cingulate cortex and amygdala activation that normalized to control levels after treatment (Fani et al., 2011; Felmingham et al., 2007; Roy et al., 2010; Simmons et al., 2013). Pre-treatment differences in hippocampal and anterior cingulate structure (Bryant et al., 2008a; van Rooij et al., 2015c) and amygdala, ACC and superior parietal lobule function (Aupperle et al., 2013; Bryant et al., 2008b; van Rooij et al., 2015b) have been shown to be markers of treatment outcome. This suggests that some neurobiological characteristics of PTSD may restore after treatment, while other features are stable markers for treatment outcome.

Here, we investigated resting state functional brain network topology in PTSD before and after treatment using graph theoretical analysis (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010). Graph theoretical analysis applied on whole brain resting state functional connectivity provides a data driven methodology for whole brain analyses, without specific a priori seed selection (Bullmore and Sporns, 2009; van den Heuvel and Hulshoff Pol, 2010). We investigate two basic network metrics that have a straightforward neurobiological interpretation: the degree and clustering coefficient. The degree of a brain region (a node) is the number of connections of a node, and represents the importance of a node in the network by functionally interacting with many other nodes (Rubinov and Sporns, 2010). The clustering coefficient reflects the interconnectedness of a group of nodes surrounding a node, and when this is high the nodes forms a cluster. A high clustering coefficient is indicative of functional segregation (Rubinov and Sporns, 2010). First, we investigated which whole brain functional network properties are associated with PTSD prior to treatment (baseline) using backward regression on PTSD patients and controls (including combat-exposed veteran controls and civilian controls). Based on previous resting state studies, we expected that network metrics of the amygdala, hippocampus, thalamus, insula, mPFC, PCC, and precuneus are associated with PTSD.

Second, a follow up scan was acquired for the patients and combat controls six to eight months after the first scan. During that interval PTSD patients received trauma-focused therapy. To investigate treatment effects we compared the network metrics associated with PTSD between patients who still had a PTSD diagnosis after treatment (persistent PTSD), patients who recover from PTSD (remitted PTSD), and combat controls. We expected to observe normalization of the network alterations to combat control levels in remitted PTSD patients, and treatment outcome-related differences.

2. Materials and methods

2.1. Participants

In total, 53 PTSD patients, 29 veteran controls (combat controls) and 26 civilian controls (healthy controls) were included, who were all male. Patients were recruited from one of four outpatient clinics of the Military Mental Healthcare Organization, The Netherlands. Patients were included after a psychologist or psychiatrist diagnosed PTSD. PTSD diagnosis was confirmed using the Clinician Administered PTSD scale (CAPS ≥45; Blake et al., 1995). The Structural Clinical interview for DSM-IV (SCID-I; First et al., 1997) was applied to diagnose comorbid disorders. A trained psychologist or PhD student administered the interviews. Control participants were recruited via advertisements, and the interviews (SCID and CAPS) were also applied to investigate PTSD symptoms and psychiatric disorders. Inclusion criteria for controls were no current psychiatric or neurological disorder, and no presence of current PTSD symptoms (CAPS ≤15).

After an interval of six to eight months 39 PTSD patients and 22 combat controls were reassessed with interviews and MRI. In order to match the civilian controls to the veteran groups on age, the civilian controls were recruited after the veterans. However, due to scanner updates during our protocol re-assessment of the civilian controls was not performed. Baseline and follow-up scans of the veteran groups were all performed before the scanner update. During the six to eight months interval patients received trauma-focused therapy, in line with Dutch and international treatment guidelines (Balkom et al., 2013; Bisson et al., 2007; Foa et al., 2000). Trauma-focused therapy included trauma-focused cognitive behavioral therapy (TFCBT) and/or eye-movement desensitization and reprocessing (EMDR), which are both effective therapeutic strategies that have similar efficacy (Bisson et al., 2007). A clinician applied the treatment (treatment as usual), and decided which strategy was applied initially. Based on PTSD diagnosis at the re-assessment according to DSM-IV criteria (American Psychiatric Association, 1994) PTSD patients were divided into a remitted group (no PTSD diagnosis at reassessment; n = 17), and a symptom persistent group (PTSD diagnosis at reassessment; n = 22). After receiving a complete written and verbal description of the study all participants gave written informed consent. The Medical Ethical Committee of the UMC Utrecht approved the study, and the study was performed in accordance with the Declaration of Helsinki (World Medical Association, 2013).

2.2. Image acquisition and pre-processing

Resting state functional magnetic resonance images were obtained on a 3.0 Tesla scanner (Philips Medical System, Best, the Netherlands: T2*-weighted echo planar interleaved images, repetition time TR = 1600 ms, TE = 23 ms, flip angle = 72.5°, field of view (FOV) 256 × 208 × 120, 30 transverse slices, 64 × 51 matrix, total scan time 8 min and 44.8 s, 0.4 mm gap, acquired voxel size 4 × 4 × 3.60 mm), where participants were asked to focus on a fixation cross, while letting their mind wander and relax. Images were pre-processed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/), and the Resting-State fMRI Data Analysis Toolkit (restfmri.net; Song et al., 2011). Pre-processing included slice-timing correction, realignment, co-registration with a T1-weighted high resolution scan acquired during the same scan session (TR = 10 ms, TE = 4.6 ms, flip angle 8°, 200 sagittal slices, FOV 240 × 240 × 160, matrix of 304 × 299), normalization, spatial smoothing (8 FWHM), de-trending, and band-pass filtering (0.01–0.08 Hz). Individuals that showed excessive motion (>2 mm in x, y, z direction or >2° in pitch, roll, yaw rotation) were excluded from analyses (three PTSD patients, one healthy control), resulting in baseline data of 50 PTSD patients and 54 controls, and data at reassessment of 39 PTSD patients and 22 combat controls. To correct for physiological noise and motion, nuisance parameters were included as regressors in the analyses (cerebrospinal fluid signal, white matter signal, and