Biological Psychology 105 (2015) 20–28

Contents lists available at ScienceDirect

Biological Psychology

journal homepage: www.elsevier.com/locate/biopsycho

The impact of depression on Veterans with PTSD and traumatic brain injury: A diffusion tensor imaging study

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ARTICLE INFO

Article history:
Received 15 May 2014
Accepted 23 December 2014
Available online 3 January 2015

Keywords:
Depression
PTSD
TBI
Emotion
DTI
Veterans

ABSTRACT

A significant proportion of military personnel deployed in support of Operation Enduring Freedom and Operation Iraqi Freedom were exposed to war-zone events associated with traumatic brain injury (TBI), depression (DEP) and posttraumatic stress disorder (PTSD). The co-occurrence of TBI, PTSD and DEP in returning Veterans has recently increased research and clinical interest. This study tested the hypothesis that white matter abnormalities are further impacted by depression. Of particular relevance is the uncinate fasciculus (UF), which is a key fronto-temporal tract involved in mood regulation, and the cingulum; a tract that connects to the hippocampus involved in memory integration. Diffusion tensor imaging (DTI) was performed on 25 patients with a combination of PTSD, TBI and DEP and 20 patients with PTSD and TBI (no DEP). Microstructural changes of white matter were found in the cingulum and UF. Fractional anisotropy (FA) was lower in Veterans with DEP compared to those without DEP.

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1. Introduction

Returning Veterans from Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) have high rates of psychiatric illness (Tanielian & Jaycox, 2008). Combat elevates the risk of both physical and psychological injuries (Hoge et al., 2004). Compared to civilians, Veterans have a higher incidence of co-morbid posttraumatic stress disorder (PTSD) (Richardson, Frueh, & Acierno, 2010; Sutker & Allain, 1996) and depression (DEP) (Bombardier et al., 2010; Brown, Fulton, Wilkeson, & Petty, 2000), present with more anger and hostility and have higher rates of completed suicides (Zivin et al., 2007). Evidence indicates military-related, delayed-onset (>6 months) PTSD is associated with higher chronicity, poorer prognosis, and resistance to treatments (Brewin, Stewart, Philpott, & Hejdenberg, 2012; Horesh, Solomon, Keinan, & Ein-Dor, 2013). Traumatic brain injury (TBI) is also a contributing factor. Rates of psychiatric disturbance following TBI are higher in military personnel than in the general population. This risk remains elevated for several decades (Ashman et al., 2004; Benotsch et al., 2000).

The co-occurrence of TBI, PTSD and DEP in returning Veterans has fueled both clinical concern and research interest. A better understanding of the unique and shared effects of these conditions could guide clinical best practices. For example, despite advances in our understanding of emotion (Gross, 2008; Gross, 2013; Joormann & Gotlib, 2010; Runnals et al., 2013) little is known about the effects of war-related illnesses on emotion regulation. Research on Veteran psychiatric illness is grossly underrepresented compared to civilians, especially in the neuroimaging literature.

We propose that studying DEP, PTSD, and TBI in Veterans presents a unique opportunity to learn how combat-specific psychiatric illness is distinct from civilian cases (Runnals et al., 2013). The neurological interaction between PTSD, DEP and TBI remains largely unknown. No empirical work exists that comprehensively evaluates the unique or shared brain impairments associated with combat-related DEP-PTSD-TBI. Our research here aimed to study the neurological profile of these co-morbid illnesses in Veterans. We used diffusion tensor imaging (DTI), neuropsychological data, behavioral assessments, and medical history to assess the unique

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http://dx.doi.org/10.1016/j.biopsycho.2014.12.011
0301-0511/Published by Elsevier B.V.

effect of DEP in Veterans also diagnosed with PTSD and TBI. We specifically asked: Does depression have an added impact on neuroanatomical integrity beyond that caused by PTSD and TBI?

1.1. Depression and DTI

Structural and functional neuroimaging studies in humans have identified an emotional brain network. They have also contributed greatly to an understanding of emotion regulatory mechanisms. Broadly defined, emotion dysregulation is high sensitivity to emotional stimuli, high emotional intensity, and a slow return of arousal to baseline. This heightened state may be driven by cognitive processes of negative appraisal or selective attention to negative environmental cues.

Emotional dysregulation is a common denominator in psychiatric illnesses like mood and anxiety disorder. Patient studies addressing the interaction between cognition and emotion agree that DEP impairs emotion regulation (Demeyer & De Raedt, 2013; Kircanski, Joormann, & Gotlib, 2012). Magnetic resonance imaging (MRI) studies support this as well. Researchers studying DEP have found a number of brain regions implicated in mood regulation, including prefrontal areas, limbic structures, and subcortical gray matter (Canli et al., 2004; Drevets et al., 1997; Hamilton, Chen, & Gotlib, 2013). Reduced cortical volumes, for example, have been documented in regions such as the anterior cingulate (Schecklmann et al., 2011), orbitofrontal (Bremner et al., 2002), anterior insular (Horn et al., 2010), and prefrontal (Schecklmann et al., 2011) cortices of patients with depression.

A developing MRI technique, diffusion tensor imaging (DTI), will likely advance these findings. DTI capitalizes on physical properties inherent in the diffusion of water molecules to assess the location, directionality, and integrity of brain white matter pathways (Assaf & Pasternak, 2008). DTI provides measures of white matter microstructure and can potentially differentiate healthy and diseased brains. One such metric is fractional anisotropy (FA). FA values quantify the direction of water's diffusion in white matter fascicles. High FA values indicate directional diffusion through structurally intact fibers. Low FA values below a certain threshold from healthy controls signals areas of clinical concern, locations where myelin and other cellular architecture have been disturbed due to shearing or degeneration. FA then serves as a potential neurocorrelate for cognitive impairment and psychological trauma.

DTI is ideally suited to evaluate the health of brain tracts and certain pathways play an important role in the pathogenesis of DEP. Specifically, loss of integrity in key cortical–subcortical tracts can lead to a "disconnection syndrome", where communication between cortical and subcortical regions is disrupted. Data from TBI patients, for example, indicates that frontal axonal injuries predispose them to emotional disinhibition and impulsive aggression (Bigler, 2008). Using voxel or region-based analyses, several DTI studies have revealed frontal and temporal white matter abnormalities in both DEP and PTSD patients (Nobuhara et al., 2006; Shimony et al., 2009; Wu et al., 2011). For example, lower FA has been reported in frontal, temporal, and parietal regions of first-episode, young adults with DEP (Ma et al., 2007). Such white matter abnormalities may be potential biomarkers of DEP pathology especially those fiber structures that are pertinent to emotion regulatory systems such as the uncinate fasciculus and the cingulum (Liao et al., 2012). Previous findings have implicated both the uncinate fasciculus and the cingulum in depression neuropathology (Zhang, Olivi, Hertig, van Zijl, & Mori, 2008; Zhang et al., 2010a, 2010b) given that both of these tracts are considered part of the limbic system and are thought to be involved in emotion processing, attention, and memory. White matter loss in the left uncinate fasciculus appears to be associated with early onset depression opposed to mid-and late-onset depression (Taylor, MacFall, Gerig, & Krishnan, 2007). Thus, a detailed examination of these tracts will likely augment our understanding of depression.

1.2. PTSD and DTI

Two studies investigated the impact of combat-related PTSD on white matter integrity. Comparing combat exposed Veterans with ($n = 6$) and without ($n = 5$) PTSD. Hedges and colleagues described white matter reductions in the temporal lobe which were significant in a multivariate test of temporal white matter as a whole, but not in post hoc analyses for specific structures within the temporal lobe (Hedges, Thatcher, Bennett, et al., 2007). In a second Veteran-specific DTI study comparing Veterans with ($n = 19$) and without ($n = 19$) PTSD, reduced values for FA were observed in the PTSD group in the bilateral prefrontal cortex, likely located in the cingulum, as well as in the bilateral posterior internal capsule and close to the angular gyrus (Schuff, Zhang, Zhan, et al., 2011). However, no differences in the uncinate fasciculus emerged in these two studies which did not report on depression comorbidity.

1.3. TBI and DTI

A DTI study by Mac Donald, Johnson, et al. (2011) included 63 U.S. military personnel who had a clinical diagnosis of mild, uncomplicated traumatic brain injury. As compared with DTI scans in controls, the scans in the subjects with traumatic brain injury showed marked abnormalities in the middle cerebellar peduncles, in the cingulum bundle and in the right orbitofrontal white matter (Mac Donald et al., 2011). No other differences were found. A second study veteran study on TBI and white matter integrity included with 25 Veterans of Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) who had been exposed during deployment to an explosive blast followed shortly thereafter by symptoms indicative of mTBI, and 33 Veterans who had not experienced an explosive blast or symptoms of blast-related mTBI. Lower FA values indicative of loss of white matter integrity was found in the forceps major and minor, bilateral anterior thalamic radiations, right corticospinal tract, bilateral inferior frontal occipital fasciculus, bilateral inferior longitudinal fasciculus and left superior longitudinal fasciculus (Davenport, Lim, Armstrong, & Sponheim, 2012). Once again, specific consideration for the impact of depression comorbidity on white matter integrity was not included in this study.

1.4. Current study

Volumetric and voxel-based DTI studies provide compelling evidence that cortical–subcortical pathways are involved in mood regulation. To further explore this, we used DTI analysis to identify whether there is a difference in regional white matter integrity (FA) for Veterans with TBI-PTSD and DEP compared to those with TBI-PTSD without DEP. Although fractional anisotropy is regarded as the standard diffusivity measure and a quantitative indicator of white matter integrity, reflecting fiber density, axonal diameter, and myelination, the present study also included measures of axial diffusivity (the degree of water diffusion along the direction parallel to the fiber bundles) and radial diffusivity (water diffusion perpendicular to the axonal wall). Our goal was to characterize the impact of DEP in patients already diagnosed with psychiatric illness and neurotrauma. We hypothesized that FA values in the group of patients diagnosed with PTSD-TBI and DEP will be decreased compared to a group without DEP. We reason this effect may be present in two association fibers connecting neuroanatomical structures implicated in emotion regulatory systems: the uncinate fasciculus (UF) and the cingulum.

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