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Evidence for disrupted gray matter structural connectivity in posttraumatic stress disorder

Susanne G. Mueller [a,*], Peter Ng [a], Thomas Neylan [b], Scott Mackin [b], Owen Wolkowitz [b], Synthia Mellon [b], Xiaodan Yan [c], Janine Flory [d], Rachel Yehuda [d], Charles R. Marmar [c], Michael W. Weiner [a]

[a] Center for Imaging of Neurodegenerative Diseases, VAMC San Francisco, Clement Street 4150, San Francisco, CA 94121, USA
[b] Department of Psychiatry, University of California, San Francisco, CA, USA
[c] Department of Psychiatry, NYU School of Medicine, New York, NY, USA
[d] Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA

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ABSTRACT

Posttraumatic stress disorder (PTSD) is characterized by atrophy within the prefrontal–limbic network. Graph analysis was used to investigate to what degree atrophy in PTSD is associated with impaired structural connectivity within prefrontal limbic network (restricted) and how this affects the integration of the prefrontal limbic network with the rest of the brain (whole-brain). 85 male veterans (45 PTSD neg, 40 PTSD pos) underwent volumetric MRI on a 3T MR. Subfield volumes were obtained using a manual labeling scheme and cortical thickness measurements and subcortical volumes from FreeSurfer. Regression analysis was used to identify regions with volume loss. Graph analytical Toolbox (GAT) was used for graph-analysis. PTSD pos had a thinner rostral anterior cingulate and insular cortex but no hippocampal volume loss. PTSD was characterized by decreased nodal degree (orbitofrontal, anterior cingulate) and clustering coefficients (thalamus) but increased nodal betweenness (insula, orbitofrontal) and a reduced small world index in the whole brain analysis and by orbitofrontal and insular nodes with increased nodal degree, clustering coefficient and nodal betweenness in the restricted analysis. PTSD associated atrophy in the prefrontal–limbic network results in an increased structural connectivity within that network that negatively affected its integration with the rest of the brain.

1. Introduction

Posttraumatic stress disorder (PTSD) is a complex reaction to life threatening or otherwise extremely stressful events that is characterized by re-experiencing symptoms in form of nightmares or flashbacks, states of hyperarousal or numbing and avoidance of trauma related situations and is typically accompanied by poor concentration and difficulty of recalling the details of the traumatic event. Evidence from functional imaging suggests that these symptoms are associated with an impaired interaction between brain regions belonging to the prefrontal–limbic network that is involved in experiencing fear, anxiety and negative emotions (Koenigs and Grafman, 2009). This network encompasses cortical regions particularly mesial and dorsolateral prefrontal and orbitofrontal regions and the insular cortex but also subcortical structures, most importantly amygdala and hippocampus but also thalamus and nucleus (ncl). accumbens regions (Francati et al., 2007; Etkin, 2009; Bremner, 2007; Cisler et al., 2013; Hughes and Shin, 2011). PTSD related abnormalities however are not only functional. Gray matter volume loss or cortical thinning have also been described and are most commonly found in the hippocampus and the mesial prefrontal cortex, particularly anterior cingulate, but occasionally also in the dorsolateral prefrontal and orbitofrontal and insular cortices (Carbo et al., 2005; Geuze et al., 2008; Woon et al., 2010; Karl et al., 2006; Eckart et al., 2011; Kuehn et al., 2011; Rauch et al., 2003; Yamasue et al., 2003), i.e., in the same regions that are affected by the functional disturbances.

Previous studies have shown evidence for a structural morphological connectivity between gray matter structures in the human brain (He and Evans, 2010; Evans, 2013; Alexander-Bloch et al., 2013), i.e., a robust and biologically plausible correlation or covariance between cortical thickness and/or gray matter volumes of anatomically and functionally linked brain areas. Regional cortical thickness or regional gray matter volume are determined by the number and size of neurons and glial cells and the degree of myelination (Carlo and Stevens, 2013; Glasser and Van Essen,

* Corresponding author. Fax: +1 415 668 2864.
E-mail address: susanne.mueller@ucsf.edu (S.G. Mueller).

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2011; Nieuwenhuys et al., 2015). The nature of the covariance of these measures across regions however is not clear and several potential factors, e.g. common afferent/efferent pathways, genetic, maturational/developmental influences, and experience related plasticity alone or in combination have been discussed in this context (Carlo and Stevens, 2013; Evans, 2013; Alexander-Bloch et al., 2013; Chen et al., 2011). Disease processes that alter cortical thickness or gray matter volume however will not only change this normal correlation pattern at the site of the primary insult but also in remote brain regions that interact with this region. In particular, the correlation strength will increase between regions that are either directly and indirectly, e.g., due to loss of input from a directly affected region, affected by the disease process and decrease between affected and non-affected regions. Based on these considerations, the overall goal of this study was to investigate if PTSD related gray matter thinning and/or gray matter volume loss within the prefrontal–limbic network would affect the structural connectivity between those structures and impact their integration into the rest of the brain.

Graph analysis provides a theoretical framework to characterize the connectivity of a network and is increasingly been used to describe the functional and structural connectivity of healthy and diseased brains (Sporns et al., 2000). It describes a network as a system of nodes and edges that connect nodes with similar properties. In terms of in vivo imaging nodes typically represent brain regions for which the property of interest, e.g. cortical thickness, time course of the BOLD signal etc, is known and the edges represent the strength of the correlation between any two regions based on the similarity of this property. The result is a correlation matrix that describes this relationship for every possible combination of regions. In order to obtain a sparse representation of the network and to eliminate edges representing weak and thus most likely irrelevant correlations, this matrix is typically thresholded at a predefined value. Several global and nodal measures can be derived to characterize the remaining connections. For this study the following measures thought to be pertinent to suspected structural pathology in PTSD (Holmes and Wellman, 2009) were chosen. Nodal Measures: a. Degree which is defined as the total number of edges that exist within the network (global degree) or the number of edges that an individual node shares with other nodes (nodal degree). Translated to structural imaging, nodal degree refers to the number of brain regions with which a region of interest shares correlations whose correlation coefficient exceeds the predefined threshold and global degree is the sum of all the pairs of regions that share supra-threshold correlations. A node representing a brain region with atrophy is more likely to have correlations exceeding the threshold and thus share edges with other nodes representing brain regions that affected by the same disease process than with nodes representing regions that are spared by the disease process (cf Supplementary Fig. and comment). b. The clustering coefficient represents the fraction of all possible connections that connect the neighbors of a given node. Although neighborhood in graph analysis refers to topological distance in the network, this often also implies anatomical neighborhood in brain structural networks based on gray matter volumes/thickness. A high clustering coefficient associated with thinning in the node or region of interest therefore indicates that the thinning extends at least to some degree to the anatomical neighbors of that region. c. Nodal betweenness centrality is defined as the fraction of all shortest paths that pass through an individual node. The path length is defined as the minimum number of unique edges connecting two nodes and thus a high nodal betweenness centrality indicates that this node is connected to many other nodes that are only one or two edges away. In healthy brains nodal betweeness centrality is therefore considered to be a measure of the importance of a node in the network. In brains with focal gray matter atrophy however, nodal betweenness centrality will also be increased in nodes in atrophied regions because the atrophy will strengthen the correlation between the region of interest with anatomically neighboring regions affected by atrophy but weaken those between the region of interest and remote regions without atrophy. Global Measures: a. Characteristic path length (lambda) is defined as the average of all nodal paths and global clustering coefficient (gamma) as the average of all nodal clustering coefficient. b. A network is considered to have a small world topology if it is characterized by a high mean clustering coefficient but relatively short characteristic path length. Small world topology is considered to represent a particularly economical network configuration because it supports segregated/specialized and distributed/integrated information processing equally well (Sporns et al., 2000; Bassett Smith and Bullmore, 2006; 2009). Disease processes impairing the structural integrity due to gray matter atrophy/thinning result in a less economical network structure and thus in a lower small world index at the whole brain network level. c. Global betweenness centrality is defined as the average of the nodal betweenness.

Based on the findings of previous volumetric studies (Karl et al., 2006), we expected to find the most prominent PTSD related gray matter volume losses in the hippocampus (restricted to subfields CA1 and dentate gyrus (McEwan, 2001) and the most prominent cortical thinning in the mesial prefrontal cortex (anterior cingulate, mesial superior frontal lobe region). Given the fact that the atrophied structures of the limbic–prefrontal network are tightly interconnected, we expected PTSD to be associated with increased structural connectivity between structures of the prefrontal–limbic network. It is important to keep in mind that the increased connectivity is associated with various degrees of atrophy within the prefrontal–limbic structures, i.e., it indicates a disruption of the prefrontal limbic network. The consequence of this local disruption, is an impaired integration of prefrontal limbic network with the non-atrophied structures of the remaining brain. Specifically we expected 1. to find signs of an increased connectivity, i.e., increased nodal degree, clustering coefficients and nodal betweenness centrality in PTSD pos compared to PTSD neg, when restricting the analysis to the limbic–prefrontal network. This atrophy was expected to increase the connectivity within the limbic–prefrontal network but to impair their interaction with non-atrophied regions/nodes outside the prefrontal network. Consequently, we expected 2. nodal degree and clustering coefficient of the limbic prefrontal nodes to be decreased in PTSD pos when analyzed within the whole brain network. The nodal betweenness centrality of the nodes in regions with atrophy though was expected to be increased in the whole brain network analysis as well due to a disproportionate loss of long and intermediate paths connecting the prefrontal–limbic region with non-atrophied regions outside compared to the mostly maintained short paths connecting it with other regions in the prefrontal–limbic network. Finally it was expected that the changes at the regional level translate into a decreased small world index as evidence for less efficient structural brain organization in PTSD at the global level.

2. Methods

2.1. Study sample

The sample consisted of 85 male veterans who had participated in Operation Iraqi Freedom (OIF) and/or Operation Enduring Freedom (OEF). They represent a subset of the first 100 subjects who were recruited for a Department of Defense sponsored multisite project that is aiming to identify reliable PTSD markers using a combination of clinical, genetic, endocrine, multi-omic and