Progress in Neuropsychopharmacology & Biological Psychiatry 77 (2017) 110–119

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

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

Resilience and cross-network connectivity: A neural model for post-trauma survival

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ARTICLE INFO

Keywords:
Resting state functional connectivity (RSFC)
PTSD
Resilience
Magnetoencephalography (MEG)
Salience Network (SN)
Default Mode Network (DMN)

ABSTRACT

Literature on the neurobiological bases of Post-Traumatic Stress Disorder (PTSD) considers medial Prefrontal cortex (mPFC), a core region of the Default Mode Network (DMN), as a region involved in response regulation to stressors. Disrupted functioning of the DMN has been recognized at the basis of the pathophysiology of a number of mental disorders. Furthermore, in the evaluation of the protective factors to trauma consequence, an important role has been assigned to resilience. Our aim was to investigate the specific relation of resilience and PTSD symptoms severity with resting state brain connectivity in a traumatized population using magnetoencephalography (MEG), a non-invasive imaging technique with high temporal resolution and documented advantages in clinical applications.

Nineteen Trauma Exposed non-PTSD (TENP) and 19 PTSD patients participated to a resting state MEG session. MEG functional connectivity of mPFC seed to the whole brain was calculated. Correlation between mPFC functional connectivity and Clinician Administered PTSD Scale (CAPS) or Connor-Davidson Resilience Scale (CD-RISC) total score was also assessed.

In the whole group, it has been evidenced that the higher was the resilience, the lower was the cross-network connectivity between DMN and Salience Network (SN) nodes. Contrarily, in the TENP group, the negative correlation between resilience and DMN-SN cross-interaction disappeared, suggesting a protective role of resilience for brain functioning.

Regarding our findings as a continuum between healthy and pathological after trauma outcomes, we could suggest a link between resilience and the good dialogue between the networks needed to face a traumatic event and its long-term consequence on individuals' lives.

1. Introduction

Post-Traumatic Stress Disorder (PTSD) is a psychiatric disorder characterized by intense fear due to the continuous reliving of the past trauma, exaggerated responses to emotionally negative stimuli, and tendency to misinterpret innocuous stimuli as potential threats (American Psychiatric Association, 2000).

The functional topography of fear processing in PTSD patients has been largely explored with functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). Due to its role in the processing of emotional stimuli and in the triggering of homeostatic neurovegetative responses to stress, amygdala activation has received special attention: increased amygdala response to emotional and neutral visual stimuli was observed in PTSD patients compared to control subjects (Lanius et al., 2006; Williams et al., 2006; Brunetti et al., 2010). Furthermore, medial Prefrontal cortex (mPFC) plays a key role in the modulation of emotional response through amygdala inhibition (Milad and Quirk, 2002; van der Werff et al., 2013; Brunetti et al., 2015). The traditional model of neural mechanisms underlying PTSD suggests that hypoactivation of the mPFC results in a loss of top-down inhibitory control and amygdalar hyper-responsivity that, in turn, generate trauma reliving and hyperarousal (Rauch et al., 2006; Patel et al., 2012). In a more recent formulation of PTSD neurocircuitry, the attention has been moved from the neural basis of fear response to the more general role of mPFC in emotion regulation, social cognition and self-referential processing (van der Werff et al.,

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http://dx.doi.org/10.1016/j.pnpbp.2017.04.010
Received 4 October 2016; Received in revised form 24 March 2017; Accepted 8 April 2017
Available online 10 April 2017
0278-5846/

2013; Patel et al., 2012). The Anterior Cingulate cortex (ACC) and mPFC activity has been observed in several studies, and their involvement in stress response, traumatic reminders, emotion regulation has also been supposed (Lanius et al., 2004; Xiong et al., 2013; Ramage et al., 2013; Reuveni et al., 2016). Furthermore, mPFC, together with Precuneus and bilateral inferior parietal cortex, represents a core region of the Default Mode Network (DMN) (Raichle et al., 2001; Fox et al., 2005). The network study, based on resting state functional connectivity, has indeed reached a growing importance for both diagnosis and prognosis. A more in-depth knowledge of this network has been suggested as a useful approach in psychiatric patients, due to its more efficient discriminatory power with respect to measurement of regional differences (Calhoun et al., 2008; Lanius et al., 2010). Specifically, disrupted functioning of the DMN has been recognized at the basis of the pathophysiology of a number of mental disorders, such as schizophrenia, anxiety, depression and PTSD (Reuveni et al., 2016; Bluhm et al., 2007; Greicius et al., 2007; Zhao et al., 2007; Broyd et al., 2009). So far, several results indicating altered within-DMN connectivity in PTSD patients have been reported (see Peterson et al., 2014 for a review). Interestingly, DMN alteration has been hypothesized to be at the basis of some PTSD symptoms, including exaggerated emotional response and misperception of benign stimuli as potential threat, because of a loss of efficiency in the internal modulation of these responses (Menon, 2011).

In the same framework, the neurocircuitry underlying several mental disorders seems to be better understood considering large-scale brain interactions between different networks. Menon, 2011 proposed that alteration in the interaction between DMN, Salience Network (SN) and Central Executive Network (CEN) may cause a maladaptive individual-environment interaction. Specifically, DMN and SN behave antagonistically during the resting state condition (Fox et al., 2005; Greicius et al., 2003; Sripada et al., 2012). Conversely, high cross-network connectivity has been observed between SN and DMN nodes during resting state in a group of earthquake survivors (Yin et al., 2011). It has also been suggested that abnormal interconnectivity between DMN and SN could contribute to some PTSD symptoms, such as hyperarousal and avoidance (Sripada et al., 2012).

More recent research on brain connectivity in psychiatric diseases has benefitted from the study of the relationships between neural biomarkers and clinical symptom scales. Several studies on PTSD moved towards this direction, relating post-trauma symptoms severity to neural correlates (Reuveni et al., 2016; Lanius et al., 2010; Dunkley et al., 2015a). In the present study, we aim at investigating the relationship between resting state large-scale network connectivity and post-trauma symptoms severity in traumatized individuals.

Since the relation between clinical scales scores and neural correlates may contribute to define the post-trauma individual profile, a special attention in this field should be paid to vulnerability and resilience measurements. Resilience refers to a dynamic process thanks to which individuals can positively adapt to a significantly adverse context, and can be able to grow despite adversities (van der Werff et al., 2013; Charney, 2004; Curtis and Cicchetti, 2003). This personal characteristic has been also defined as a multidimensional phenomenon, encompassing internal locus of control, social problem-solving skills, sense of meaning, and self-esteem (Daniels et al., 2012). The incidence of PTSD in the general population is low. When it is confronted with a traumatic episode, a minor part of subjects develops PTSD symptoms, whereas a spontaneous recovery occurs in a large part of the population (van der Werff et al., 2013). Among the individual differences, resilience represents the personal characteristic that could contribute to a positive post-trauma outcome. The comprehension of the neural mechanisms at the basis of resilience may provide valuable tools for prevention and treatment of post-trauma diseases. In his model of allostasis, Charney (2004) isolated eleven neurochemical, neuropeptide and hormonal possible mediators of the psychobiological response to stressors. Furthermore, the author examines the neural mechanism mediating reward, fear conditioning and social behavior circuits that are considered to be relevant to the character traits linked to resilience (Charney, 2004). Interestingly, as the author highlighted, the mPFC is the only brain structure involved in all three circuits. Nevertheless, a restricted number of studies searched a relationship between resilience and brain functioning. In an fMRI study on healthy subjects, Waugh et al. (2008) showed that participants with high-trait resilience exhibited a lower Insular activity with respect to the low-trait-resilience group in response to neutral stimuli following a threat cue, thus suggesting a rapid and appropriate evaluation of the neutral information (Waugh et al., 2008). Another fMRI and perspective study investigated the predictive value of resilience for PTSD development, and the neural correlates underpinning the relation between resilience and post-trauma recovery in an acutely traumatized population (Daniels et al., 2012). The authors found that resilience predicted PTSD symptoms at 5–6 weeks and at 3 months. Furthermore, they measured the relation between resilience score and BOLD response during trauma recall, revealing a significant relationship between trait resilience and right thalamus and inferior frontal gyrus, both involved in emotion regulation.

Finally, in his review, van der Werff proposed a model of functional and structural circuits putatively involved in resilience, highlighting that, among the studies on traumatized individuals, an overlapping could be observed between the neural circuit of resilience and the one involved in emotion regulation (van der Werff et al., 2013). The author supposed that, from a functional point of view, an increased emotion upregulation (induced from mPFC) could be at the basis of individual resilience. Furthermore, this review indicates that the connectivity between amygdala-prefrontal cortex and other networks such as DMN or SN could play a primary role in resilience.

Considering on one hand the medial Prefrontal cortex key role in emotion regulation and resilience, and, on the other hand, the potential insight coming from the study of large scale network connectivity, an interesting contribution to the understanding of post-trauma recovery could be represented by the investigation of the relationship between resilience and resting state functional connectivity (RSFC) of mPFC, as a DMN node, with other networks. Nevertheless, to the best of our knowledge, no studies that directly correlate resting state functional connectivity to resilience have been so far conducted in a traumatized sample. Furthermore, the great majority of RSFC studies in PTSD have been carried on with fMRI, while only a few resting state magnetoencephalography (MEG) studies have been so far performed on PTSD.

MEG is a non-invasive high-resolution imaging technique whose advantages in clinical applications have been documented (Wilson et al., 2016). In the past decade, the improvement of instruments and modeling technique developed in this field allowed a promising growth of MEG application to the characterization of neural mechanisms at the basis of several mental diseases. To date, findings from MEG resting state studies suggest atypical long-range hyperconnectivity in the high gamma band of resting state networks in PTSD patients compared to traumatized controls (Dunkley et al., 2014). Interestingly, another study by the same group revealed that PTSD severity positively correlated with gamma synchrony within the SN (Dunkley et al., 2015b). These data encourage the use of MEG to look for MEG-based PTSD biomarkers, mainly connecting MEG results with clinical symptoms (Wilson et al., 2016). Moreover, pharmaco-MEG, based on the changes in neuronal processing, induced by drug chemical neuromodulation and measurable on the millisecond time-scale, has been successfully used in patients to understand brain pathologies and drug-treatment effects (Muthukumaraswamy, 2014).

The present MEG study aims at directly investigating the relationship of resting state functional connectivity between the anterior frontal node of DMN (mPFC) and the whole brain with resilience, as measured by means of the Connor-Davidson resilience scale (CD-RISC) (Connor and Davidson, 2003), and PTSD severity according with Clinician Administered PTSD Scale (CAPS) (Blake et al., 1995) in PTSD patients