A Network-Based Neurobiological Model of PTSD: Evidence from Structural and Functional Neuroimaging Studies

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Abstract

Purpose of Review—Although a fine-grained understanding of the neurobiology of posttraumatic stress disorder (PTSD) is yet to be elucidated, the last two decades have seen a rapid growth in the study of PTSD using neuroimaging techniques. The current review summarizes important findings from functional and structural neuroimaging studies of PTSD, by primarily focusing on their relevance towards an emerging network-based neurobiological model of the disorder.

Recent Findings—PTSD may be characterized by a weakly connected and hypoactive default mode network (DMN) and central executive network (CEN), that are putatively destabilized by an overactive and hyperconnected salience network (SN) – which appears to have a low threshold for perceived saliency, and inefficient DMN-CEN modulation.

Summary—There is considerable evidence for large-scale functional and structural network dysfunction in PTSD. Nevertheless, several limitations and gaps in the literature need to be addressed in future research.

Keywords

posttraumatic stress disorder; default mode network; central executive network; salience network; functional magnetic resonance imaging; structural MRI

Introduction

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric illness that is characterized by persistent symptoms of re-experiencing, avoidance of trauma-related stimuli, negative thoughts and feelings, and arousal and reactivity, that develops in certain individuals in the aftermath of a traumatic event [1]. Prevalence rates of PTSD are estimated at 6.8% in the

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general population in the United States [2] and at 23% in US Veterans [3]. A fine-grained understanding of the neurobiology of PTSD is yet to be elucidated. However, the last two decades have seen a rapid growth in the study of PTSD using neuroimaging techniques, that were made possible by considerable advancements in the technology and methods.

Advances in functional neuroimaging methods, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT), have enabled the exploration of dynamic neural changes involved in the pathophysiology of PTSD. In PET and SPECT, a radioactive tracer is administered to quantify regional brain metabolism or regional cerebral blood flow, providing a measure of neuronal activity. In contrast, fMRI is based on the intrinsic blood-oxygen-level dependent (BOLD) signal and does not require the administration of a tracer. By measuring regional metabolic or blood flow changes, PET and SPECT inherently provide a more direct estimates of neuronal activation; while in fMRI, several techniques have been developed to indirectly quantify this activity. For example, the amplitudes of low-frequency fluctuations (ALFFs) of the BOLD signal can be quantified as a measure of intrinsic regional activity. Several meta-analyses have pooled multi-modal brain activation studies (PET, SPECT, and fMRI) using an activation likelihood estimation (ALE) approach, which may provide a more confirmatory evidence to complement findings from individual studies [4–7]. In addition to activation studies, functional connectivity has been also employed in the study of psychopathology. Functional connectivity usually refers to a functional coupling or association (e.g. Pearson correlation, granger causality) between time series extracted from different voxels or *regions-of-interest* (ROIs). The structural characteristics of the brain can be assessed using structural MRI (sMRI). To date, the majority of sMRI studies in PTSD have focused on volumetric gray matter (GM) alterations, but a growing body of research includes measures such as cortical thickness, and morphometry. Finally, white matter tract connectivity and integrity can be studied using diffusion MRI (dMRI), which capitalizes on the diffusion of water molecules to create a contrast in the images, therefore identifying membrane-bound fibers (i.e., axons). The constraint of the movement of water molecules along a longitudinal tract can be quantified as fractional anisotropy (FA), where lower values may reflect impaired overall integrity of white matter tracts.

As part of a Special Issue on PTSD, this selective review will summarize important findings from functional and structural neuroimaging studies of PTSD, by primarily focusing on their relevance towards an emerging network-based neurobiological model of the disorder [8]. The readers are referred to [9–13] for complementary and alternative neurobiological models of PTSD, and to [14, 7, 4–6] for more comprehensive systematic reviews and meta-analyses.

Network-Based Neurobiological Model of PTSD

Traditionally, evidence of brain alterations in PTSD have been presented under a fronto-limbic model that includes the amygdala, medial prefrontal cortex (mPFC), and hippocampus as core implicated structures. This model stipulates that an overactive amygdala is responsible for heightened arousal and exaggerated fear, aggravated by loss of top-down inhibition due to a dysfunctional mPFC; the hippocampus integrates into this

picture by failing to identify safe or otherwise non-threatening situations thereby contributing to avoidance and re-experiencing (referred to in the hippocampal literature as *pattern separation*) [15]. Indeed, several lines of evidence from different imaging techniques have corroborated a disruption within these structures [9].

However, it is becoming increasingly clear that the scope of the functional abnormalities requires a broader approach to better capture the complexity of the disorder. Compelling evidence suggests that the brain is organized into functionally distinct brain networks with high intrinsic connectivity—dubbed *intrinsic connectivity networks* (ICNs) [16]. ICNs are identified using data-driven decomposition methods, and therefore their identification does not require a priori hypotheses [16]. Rather than constraining this review to alterations within discrete structures under the traditional fronto-limbic neurocircuitry model of PTSD, we attempt to present the evidence of functional alterations in the broader framework of large-scale network dysfunction (see Figure 1 & Table 1). Generally, in PTSD, the vast majority of the evidence has fallen under one of three of such networks. They are known as the default mode, central executive (also referred to as *frontoparietal control*), and the salience (also referred to as *ventral attention*) networks. Collectively, disruption in these three networks has been dubbed the *triple network model* by Menon [8].

One of the most robustly identifiable networks is known as the default mode network (DMN). In contrast to most ICNs, the DMN exhibits relative hypoactivity during cognitive and stimulus-driven tasks, and is most active at rest. Indeed, some of the main functions of the DMN are thought to involve self-referential thought and other introspective processes— activities that predominantly occur at rest. Structurally, this network consists of core regions in the posterior cingulate cortex (PCC), ventromedial prefrontal cortex (vmPFC), and medial temporal lobe (MTL; including the hippocampus) [17]. Although ICNs constitute *functionally*-coupled entities by definition, structures of the DMN seem to additionally exhibit strong structural interconnections, highlighting the evolutionary importance of this network [18]. Given the known manifestations of intrusive symptoms, dissociation, and avoidance in PTSD [1], it is possible that a dysfunction in core structures of the DMN, or functional or structural dysconnectivity between these structures, may mirror these behavioral changes [8].

The central executive network (CEN), is active during cognitively demanding tasks, goal-directed behavior, and cognitive control of emotions, and is centered around the dorsolateral prefrontal cortex (dlPFC), encompassing the middle frontal gyrus, precuneus, and parts of the premotor cortex [8, 16]. A disrupted CEN may contribute to the cognitive and memory deficits, and the loss of top-down emotional control observed in PTSD [8].

The salience network (SN) is involved in the detection of salient internal and external stimuli. Core structures that are part of the SN are the amygdala, insula, and dorsal anterior cingulate cortex (dACC) [8]. Within the SN, based on the perceived threat level, the anterior insula is thought to arbitrate/modulate the dynamics between CEN and DMN (switching between task-relevant and task-irrelevant behavior), and effective connectivity analyses have inferred its causal control over these two networks in the normal brain [8, 19]. Consequently,

aberrancy in the SN may alter these threat-detection functions, and could underlie behaviors such as hyperarousal [8].

Evidence from Structural and Functional Neuroimaging Studies

Default Mode Network

Resting-state ROI-to-ROI fMRI connectivity studies have demonstrated a decreased coupling between known structures of the DMN in PTSD, such as the vmPFC-hippocampus [20], PCC-hippocampus [21, 22], and PCC-vmPFC [21], often correlating with symptom severity. DMN functional dysconnectivity has also been replicated using approaches other than ROI-to-ROI connectivity. Using a more comprehensive representation of the DMN and graph theoretical analysis, one study showed a decrease in overall connectivity strength in the PTSD group [23]. Another study made use of signal decomposition methods and found evidence of decreased affinity of the PCC to the rest of the DMN during an autobiographical memory task [24]. With regard to structural connectivity in PTSD, reduced FA has been described within the white matter of the vmPFC region [25], in the white matter linking vmPFC to PCC (i.e., cingulum bundle) [26–28], and in the white matter linking the vmPFC to the hippocampus [29, 30]. These findings suggest that the structural changes may at least partly contribute to the alterations observed at the functional level. Structurally, localized GM reductions (i.e., volume or thickness) have been described in the vmPFC [31], PCC [32], MTL [32–34], and hippocampus [35]. Functional imaging data here shows vmPFC and PCC hypoactivity across a range of symptom provocation and cognitive-emotional studies [5, 6], and during resting-state (although less consistently) [7, 4].

With regard to functional activity in the hippocampus, the bulk of the evidence has shown increased activation in PTSD, though a number of studies have reported hypoactivation as well [5, 6]. The hippocampus is a functionally and structurally heterogeneous brain region and performs several functions. A particularly relevant division is along its long axis. The anterior part of the hippocampus is implicated in stress response, emotion-related memory, and pattern completion, mediated via strong connections to the amygdala [36, 37]; while the posterior portion is thought to be more involved in spatial functions, and pattern separation, and is anchored in the DMN-proper [37, 17]. Focused structural (shape and volumetric) alterations in the anterior hippocampus have been described in the literature [38, 39], and in specific hippocampal subfields (e.g., cornu amonis 3, and dentate gyrus) [9, 40]. A pattern of functional dysconnectivity between anterior hippocampus and the rest of the brain is also emerging [41]. Moreover, while the majority of ROI activation studies did not make the distinction between anterior vs. posterior hippocampus, the hippocampal activation cluster that was identified in a whole-brain meta-analysis in PTSD was located anteriorly [6]. Here, hyperactivity could be a reflection of intrusive recollections and a disruption in the extinction process [42].

Fewer studies have reported on the posterior hippocampus. In a resting-state connectivity study, the posterior (but not anterior) hippocampus was found to have decreased connectivity to other regions primarily in the DMN (PCC, vmPFC, precuneus) in the PTSD group [43]. Another study found a loss of differentiation in anterior vs. posterior functional connectivity profile in the PTSD group compared to controls [44]. Here, future ROI activation studies

that make the distinction between the different parts of the hippocampus will be helpful in informing whether there is a differential activation pattern.

Response to therapy has been linked to normalization of DMN abnormalities in some studies. For example, a trial of paroxetine in patients with PTSD showed an association between increased hippocampal volume post-treatment and overall symptom improvement [45]. Similarly, the response to psychotherapy has been linked to normalization in structural changes in the rostral ACC [46–48], hippocampus [49, 50], and PCC [32]. However, it remains unclear whether different types of therapy are associated with specific changes. To date, response to both cognitive behavioral therapy and prolonged exposure therapy has been linked to rostral ACC [51, 46] and hippocampal [49, 51] GM increases. Conversely, an increase in the GM of the PCC may be more specific to response to eye movement desensitization and reprocessing therapy [32].

Central Executive Network

Although the CEN remains generally under-investigated in PTSD, there is evidence of weaker functional connectivity within the CEN. A decreased connectivity between the premotor cortex and dlPFC (middle frontal gyrus) was associated with increasing trauma exposure, while the reduced connectivity between premotor cortex and parietal cortex/ middle frontal gyrus was associated with increased PTSD symptom severity [52]. In another fMRI connectivity study involving an autobiographical memory task, the CEN in PTSD patients showed decreased ability to recruit the precuneus [24]—another structure of the CEN. Connectivity between the CEN and the DMN also appears to be crucial, as increased dlPFC to PCC resting-state connectivity has been linked to response to mindfulness-based exposure therapy [53].

In PTSD, the dlPFC shows hypoactivity at rest [4], and across several cognitive-emotional tasks [6]. In contrast, other regions such as the precuneus may be hyperactive under emotional tasks [6]. These findings have been paralleled in the sMRI literature with evidence showing reduced dlPFC thickness in PTSD in cross-sectional studies [54–57]. In a longitudinal study of trauma victims, increased dlPFC thickness was found approximately one year after trauma [58]. Moreover, greater dlPFC thickness initially was linked to later symptom reduction, earlier improvement, and gradual cortical thickness normalization later in the course (the cohort remained largely treatment-naïve throughout the study) [58]. The discrepancy between the cross-sectional and longitudinal studies could be due to assessment at different time points, and highlights the relevance of studying PTSD chronicity. Congruent with the findings from the longitudinal study, white matter FA in the dlPFC appears to be increased in PTSD [59].

Taken together, these findings suggest that an increased emotional-modulation burden on the CEN immediately after trauma could lead to compensatory increase in dlPFC cortical thickness and white matter FA. Functionally, the CEN may be invested in modulating outside ICNs (e.g., SN; see *Salience Network*) in order to dampen/compensate for trauma-induced changes in these networks (e.g., SN/amygdala hyperactivity). The outwards investment of the CEN comes at the expense of decreased within-CEN functional connectivity and hypoactivity, which could manifest as cognitive and attentional symptoms.

With recovery from PTSD, less demand on the CEN induces normalization (i.e., reduction) in dlPFC thickness. This is consistent with the known role of the CEN plays in top-down control [42].

Salience Network

Increased functional coupling, or ROI-to-ROI connectivity between paired regions of the SN, such as amygdala-insula [60, 20], and amygdala-dACC [61] has been generally described in PTSD at rest. In contrast, decreased connectivity between the dACC and the rest of the SN was reported during an autobiographical memory task [24]. Increased insula-hippocampus [20] and amygdala-vmPFC [61] connectivity at rest have been described and represent increased SN-DMN connectivity. Furthermore, during an autobiographical memory task, PTSD was associated with an aberrant recruitment of the amygdala into the DMN (rather than the SN) [24]. Finally, increased SN to CEN coupling was also evident in PTSD under a threat processing paradigm [62]. Within PTSD, individuals with the dissociative-subtype (PTSD+DS) appear to exhibit increased amygdala-dlPFC and amygdala-PCC connectivity compared to individuals with non-dissociative PTSD (PTSD-DS) [63].

One of the most replicable findings in functional studies of PTSD has been increased amygdala activity. This finding has been captured both at rest, and across different task paradigms [4–6]. The dACC, unlike the ventral or dorsolateral regions of the PFC, is also hyperactive in PTSD [6]. This is not surprising given the affiliation of the dACC to the SN (in contrast the vmPFC is part of the DMN, and the dlPFC is part of the CEN) [8]. In the insula, there have been some mixed results with regard to its activity in PTSD [5]. Yet, a pattern is emerging where the anterior part show increased activity at rest and under various emotional and cognitive paradigms, while the posterior insula appears to be hypoactive [4, 6, 7]. This is better understood in the context of evidence that implicate the anterior insula in functions such as the arbitration between the CEN and DMN, and the regulation of physiological changes during social-emotional tasks (anteroventrally; via connections to the amygdala) and cognitive-executive tasks (anterodorsally) [64, 19]. In contrast, posterior portions of the insula predominantly involve somatomotor functions [64]. Structurally, the integrity of core elements of the SN has been shown to be altered in PTSD. This is characterized by GM alterations in the amygdala [65–67], GM reductions in the dACC [68, 14, 31]; and abnormalities in the insula. The latter is evident by decreased GM [31], cortical thickness [57, 69], and FA in the white matter [25], as well as by increased betweenness centrality [69]—a measure of the importance of a particular node in the network.

Increased functional coupling and hyperactivity within the SN at rest may indicate a state of "primed" saliency. Weakened connectivity between the dACC and the rest of the SN becomes evident during tasks (e.g., autobiographical recall), potentially indicating a disrupted top-down inhibition under challenge. Exaggerated SN function could disrupt its ICN arbitration role, which is evident by increased SN-DMN and SN-CEN connectivity. Increased SN-CEN connectivity could alternatively be reflecting an augmented compensatory CEN top-down function aimed at dampening SN hyperactivity (though the two possibilities are not mutually exclusive). Furthermore, increased SN-CEN functional

dysconnectivity in PTSD+DS vs. PTSD-DS may potentially represent emotional overmodulation in dissociative PTSD [70].

A summary of the evidence for the network-based model has been provided in Table 1.

Conclusions and Limitations

Overall, there is considerable evidence for large-scale network dysfunction in PTSD. Altered dynamics within, and between the DMN, CEN, and SN are potentially capable of accounting for the varying and heterogeneous endophenotypes of the disorder. Generally, PTSD may be characterized by a weakly interconnected and hypoactive DMN, putatively destabilized by an overactive and hyperconnected SN. The latter appears to have a low threshold for saliency, and to be incapable of efficient DMN-CEN modulation. Abnormalities within the CEN may underlie some of the cognitive, executive, and emotional regulatory dysfunctions in PTSD. An enhanced CEN to DMN connectivity, which has been linked to treatment response, may be an acquired resilience or bypass mechanism by which trauma-exposed individuals adapt to/overcome a specific circuit or nodal aberrancy.

The chain of events and the causal interactions between these networks has not been studied in PTSD, and may be crucial in forming a more complete understanding of the mechanism behind the disorder. Furthermore, it is unclear if structural changes underlie the functional abnormalities, or whether the chronicity of the functional abnormalities induces long-term structural changes [71]. Longitudinal multi-modal studies will be crucial in informing such questions. Several limitations in neuroimaging studies limit the interpretability and generalizability of the findings. Within the same imaging modality, different first-level processing pipelines result in considerable heterogeneity, and to date, no consensus has been reached for a "golden standard" that balances between sensitivity to detect subtle changes on one hand, and improved resistance to noise/artifact on the other (e.g., test-retest performance). Since the majority of the functional connectivity literature in PTSD consists of ROI-to-ROI studies, we had to approximate ICN-level changes from discrete ROI-to-ROI observations. It is important to note that single ROIs oftentimes do not represent the entirety of the ICNs in question (e.g., using dlPFC to PCC connectivity as a surrogate for CEN-DMN connectivity may be providing an incomplete picture). A more refined approach could entail using validated brain-parcellation atlases, combined with parcel-to-ICN affiliation information, and graph theory tools to study whole-ICN connectivity [23, 72]. Other approaches that are also devoid of this limitation include the use of decomposition methods (e.g., independent component analysis) to compare the spatial extent of different ICNs (in this context, the interpretability of "reduced spatial extent of the DMN" would be analogous to "decreased connectivity within the DMN") [24]. Both of these approaches may provide essential information, complementing the findings from ROI-to-ROI connectivity studies. Task paradigms during imaging acquisition, which range from resting-state to symptom provocation, are a powerful way to probe various cognitive-emotional processes. Nonetheless, they may hinder generalizability of the findings and their replication across studies. This shortcoming could be addressed in the future by developing standardized "stress tests" of psychopathology, which preferably would consist of a battery of tasks aimed at highlighting changes within and across psychiatric disorders.

Although not specifically a shortcoming of imaging techniques, the choice of the comparator group (i.e., matched healthy vs. trauma-exposed control) has a number of implications that have not been addressed in this manuscript. Unifying the sample under a traumatic event may serve as a common ground to selectively probe dysfunctional trauma-induced changes. However, trauma-exposed individuals who do not develop PTSD may be a particularly resilient group with pre-exposure protective factors. They may also be characterized by post-trauma resilience-conferring behavioral and brain changes. This may affect the interpretability of results and may increase the prospect of confounding factors.

For example, one study found that increased ACC volume may be a trait-like marker for a person's ability to recover from trauma because it predicts improvement of PTSD symptoms but does not change during or after treatment [47]. An investigation of trauma survivors who had not developed PTSD in the eight years following the event found significantly greater cortical thickness in several areas of the temporal lobe compared to controls, suggesting that hypertrophy of the cortex may be either a premorbid protective factor, or a resilience-related development following trauma [73]. As previously mentioned under *Central Executive Network*, a longitudinal study of victims of a subway arson attack showed that trauma-exposed victims with PTSD had significantly increased cortical thickness in the dlPFC compared to trauma-naïve controls approximately 1 year following the trauma. Further, the larger this cortical thickness increase, the greater the ensuing reduction of PTSD symptoms [58]. Collectively, the data suggests that the dorsolateral PFC may not only increase in response to trauma and/or PTSD, but that this may be an adaptive structural alteration which, could promote healing after a traumatic event. As the field continues to investigate the etiology and resultant pathophysiology of PTSD, additional possible protective factors may be identified.

Another clinically-relevant question is whether the brain abnormality findings represent a premorbid vulnerability to develop PTSD, or are instead a consequence of the disorder (covered in detail in the following reviews [74, 75]). This growing body of evidence suggests that some regions (such as the hippocampus) may at least partially predispose vulnerability for PTSD [76–78], while others (like portions of the ACC) may be a consequence of the neurotoxic effects of chronic stress in those who develop PTSD following a trauma [79]. In general, current imaging-derived neurobiological models of PTSD are largely based on cross-sectional studies that lack multiple assessments over time within a longitudinal experimental design. Furthermore, participants in imaging studies that focus on PTSD related to childhood trauma are usually adults whose brains have matured. Any comprehensive model of PTSD-related structural and functional brain abnormalities should also include developmental data obtained on traumatized children, since childhood trauma and PTSD appear to manifest differently in the pediatric brain [80] (See review by Herringa elsewhere in this Special Issue [81]).

While the triple network model provides a framework to understand psychopathology, it is unlikely to account for all PTSD abnormalities. Thus, it is important for the field to continue pursuing data-driven exploratory methods. For example, one structure that did not received much attention in PTSD but has been repeatedly implicated by model-free whole-brain meta-analyses, is the cerebellum [4, 7, 5]. Although there has been a recent increased

interest in this structure [82, 83], the specific role of the cerebellum in stress-related psychopathology is yet to be fully elucidated.

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Salience Network

dACC, amygdala, insula

↑ activity and intrinsic connectivity

- Heightened threat-detection (hyperarousal)
- Impaired DMN and CEN modulation

Central Executive Network

dlPFC, precuneus

↓ activity and intrinsic connectivity

- Cognitive deficits
- Loss of top-down SN regulation

Default Mode Network

vmPFC, PCC, MTL

↓ activity and intrinsic connectivity

- Disrupted internal mentation (intrusive symptoms, re-experiencing)
- Altered sense of self/reality (dissociation)
- Fear generalization (avoidance)

Figure 1. Network-based neurobiological model of PTSD

The figure shows the cortical representations of the salience network (SN; orange), default mode network (DMN; red), and central executive network (CEN; blue) in healthy individuals [16]; notable region-of-interests (ROIs) within these networks; the changes in PTSD predicted by the model; and the putative resulting phenotypic abnormalities. Alterations within and between the SN, CEN, and DMN may underlie the psychopathology of PTSD. According to this model, the SN is hyperconnected and hyperactive and has a low threshold for perceived saliency (underlying symptoms of hyperarousal), and is incapable of efficient DMN-CEN modulation (i.e. switching between task-relevant and task-irrelevant behavior); the CEN is a weakly interconnected and hypoactive (paralleling impaired cognition), and is incapable of top-down SN regulation; finally, the DMN is a weakly interconnected and hypoactive resulting in disrupted ability to maintain a calm inner state (intrusive symptoms), altered sense of self/world (dissociation), and fear generalization

(avoidance; mediated by the hippocampus). * Denotes altered between-network connectivity.

Table 1

Summary of neuroimaging findings in PTSD

	Intrinsic Fc	Functional Activity	Between-network Fc	WM	GM
DMN	↓ vmPFC-hippocampus [20], vmPFC-posterior hippocampus [43], PCC-posterior hippocampus [43], PCC-hippocampus [21], PCC-vmPFC [21], hippocampus overall [23], PCC-vmPFC-MTL [24]	↓ vmPFC, PCC [5–7, 4] ↓↑ hippocampus [5, 6] ↑ anterior hippocampus [6]	↑ Increased insula-hippocampus [20], amygdala-vmPFC [61]	↓ FA in cingulum (vmPFC-PCC) [26–28] ↓ FA in vmPFC-hippocampus [29, 30] ↓ vmPFC [25]	↓ vmPFC [31], PCC [32], MTL [32–34], hippocampus [35] ↓ anterior hippocampus [38, 39]
CEN	↓ premotor cortex-dlPFC, premotor cortex- parietal cortex/middle frontal gyrus [52], precuneus-CEN [24]	↓ dlPFC [4, 6] ↑ precuneus [6]	↑ SN-CEN coupling [62]	↑ FA in dlPFC [59]	↑↓ dlPFC [54–57]
SN	↑ amygdala-insula [60, 20], amygdala-dACC [61] ↓ dACC-SN [24]	↑ amygdala [4–6], dACC [6], anterior insula [4, 6, 7]	–	↓ FA in insula, cingulum [25–27]	↓↑ amygdala [65–67] ↓ dACC [68, 14, 31], insula [31, 57, 69]

Abbreviations — Fc: Functional Connectivity; WM: White Matter; GM: Gray Matter; DMN: Default Mode Network; CEN: Central Executive Network; SN: Salience Network; vmPFC: Ventral Prefrontal Cortex; PCC: Posterior Cingulate Cortex; MTL: Medial Temporal Lobe; FA: Fractional Anisotropy; dlPFC: Dorsolateral Prefrontal Cortex; dACC: Dorsal Anterior Cingulate Cortex.