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Citation	Mohan, Akansha, Aaron J. Roberto, Abhishek Mohan, Aileen Lorenzo, Kathryn Jones, Martin J. Carney, Luis Liogier-Weyback, Soonjo Hwang, and Kyle A.B. Lapidus. 2016. "The Significance of the Default Mode Network (DMN) in Neurological and Neuropsychiatric Disorders: A Review." <i>The Yale Journal of Biology and Medicine</i> 89 (1): 49-57.
Citable link	http://nrs.harvard.edu/urn-3:HUL.InstRepos:26318604
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The Significance of the Default Mode Network (DMN) in Neurological and Neuropsychiatric Disorders: A Review

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The relationship of cortical structure and specific neuronal circuitry to global brain function, particularly its perturbations related to the development and progression of neuropathology, is an area of great interest in neurobehavioral science. Disruption of these neural networks can be associated with a wide range of neurological and neuropsychiatric disorders. Herein we review activity of the Default Mode Network (DMN) in neurological and neuropsychiatric disorders, including Alzheimer's disease, Parkinson's disease, Epilepsy (Temporal Lobe Epilepsy - TLE), attention deficit hyperactivity disorder (ADHD), and mood disorders. We discuss the implications of DMN disruptions and their relationship to the neurocognitive model of each disease entity, the utility of DMN assessment in clinical evaluation, and the changes of the DMN following treatment.

INTRODUCTION

Functional or resting state connectivity studies that assess the integration of activity across distant brain regions provide insight into the intrinsic connectivity networks (ICNs), particularly the Default Mode Network (DMN), which is the most well-characterized ICN [1,2].

The DMN became a focus of neuroscientific interest following findings that activation in a constellation of brain areas was reduced during task-related activities or when executive function was required [1,3]. These areas include the precuneus/posterior cingulate cortex (PCC), medial prefrontal cortex (MPFC), and medial, lateral, and inferior parietal cortex.

The DMN includes brain regions with high degrees of functional connectivity and is active in the brain at rest, but becomes deactivated when task performance is initiated. The resting state activity has been termed the default-mode of brain activity to denote a state in which an individual is awake and alert, but not actively involved in an attention-demanding or goal-directed task [2,4].

While several approaches can investigate the DMN, the most widely used methodology uses Resting State Functional Magnetic Resonance Imaging (RS-fMRI) [5]. Functional Magnetic Resonance Imaging (fMRI) can detect the Blood Oxygenation Level-Dependent (BOLD) signal in a variety of brain

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†Abbreviations: ICNs, intrinsic connectivity networks; DMN, Default Mode Network; PCC, precuneus/posterior cingulate cortex; MPFC, medial prefrontal cortex; RS-fMRI, Resting State Functional Magnetic Resonance Imaging; fMRI, Functional Magnetic Resonance Imaging; BOLD, Blood Oxygenation Level-Dependent; ICA, independent components analysis; AD, Alzheimer's disease; PD, Parkinson's disease; ADHD, attention deficit hyperactivity disorder; CEN, central executive network; TLE, Temporal Lobe Epilepsy; IEDs, interictal epileptic discharges; IGE, idiopathic generalized epilepsy; MDD, major depressive disorder; BD, bipolar disorder

Keywords: Default Mode Network, Resting State Functional Magnetic Resonance Imaging, Alzheimer's disease, Parkinson's disease, Temporal Lobe Epilepsy, mood disorder, attention deficit hyperactivity disorder

regions as a proxy for neural activation. In this context, blood flow changes appear to reflect neural activity changes in brain tissue [6]. Because RS-fMRI measures the BOLD signals when an individual is not engaged in any task-related brain activity [5], it can be applied to study the DMN.

In a seed-based approach, where an area of interest is chosen and its time course of activation is compared to that of other regions in the brain, a threshold is set to identify voxels significantly correlated with that area of interest [7]. Regions whose time courses of activation are highly correlated are considered to be in the same network. However, this approach requires *a priori* selection of the area of interest [7].

Another popular method is independent component analysis (ICA), a computational technique that separates complex signals from multiple sources. For RS-fMRI data, ICA can be used to spatially identify distinct resting state networks by decomposing the fMRI data set into time courses and associated spatial maps. Compared to seed-based methods, ICA has advantages of requiring few *a priori* assumptions and not needing the user to manually select the important components or distinguish noise from physiological signals [7]. Despite differences between the two approaches, results from seed-based analyses and ICA have yielded similar results in healthy subjects [8].

Since its discovery, interest has grown in the clinical utility and implications of the DMN [1,4,9,10]. The clinical significance of the DMN has been established or implicated in neurological and neuropsychiatric disorders [4,11-15]. This may be related to potential roles of the DMN, including the consolidation of memory [16], working memory [17-21], broad-based continuous sampling of external and internal environments [2,4], processing of emotionally-salient stimuli [22], and the interplay between emotional processing and cognitive functions [2,23,24].

As understanding of the clinical implications of DMN changes in various neurological and neuropsychiatric disorders grows, reviewing the current literature can help consolidate knowledge from multiple studies. Herein, we focus on reviewing neurological and neuropsychiatric disorders in which clinical significance of the DMN has been suggested. These disorders include Alzheimer's disease (AD), Parkinson's disease (PD), epilepsy (especially Temporal Lobe Epilepsy), attention deficit hyperactivity disorder (ADHD), and mood disorders. Additional studies utilizing RS-fMRI are discussed when they provide important additional insight into the DMN findings in these disorders.

ALZHEIMER'S DISEASE (AD)

AD is a neurocognitive disorder associated with the abnormal accumulation of protease-resistant proteins (e.g., amyloid- β and hyper-phosphorylated tau) forming

amyloid plaques and neurofibrillary tangles in the brain [25,26], which leads to progressive synaptic, neuronal, and axonal damage and presents with cognitive impairments and memory disturbance. By the time AD is strongly suspected, more widespread cognitive deficits and behavioral disturbances in multiple domains are often observed. Lifestyle (e.g., diet and exercise) and genetic factors (e.g. Apolipoprotein-E genotype) influence brain changes and therefore may affect the timing of AD onset [27].

The hypothesis that DMN activity during rest is necessary for memory consolidation suggests a potential connection with the development of AD [16]. Decreased functional connectivity in the DMN of patients with AD has been consistently demonstrated, especially between posterior (precuneus and posterior cingulate cortex) and anterior (anterior cingulate cortex and medial prefrontal cortex) regions [28-31]. Changes in functional connectivity of regions within the DMN have also been found in individuals at high risk of developing AD [28,29,31-36], suggesting that these changes may provide potential biomarkers for AD. Interestingly, functional connectivity disturbances in the DMN have been found to overlap with patterns of amyloid deposits in patients with AD [16,37,38].

In addition, functional connectivity can be used to track changes in the DMN of patients with AD after pharmacologic treatment [16]. Lorenzi et al. examined AD patients before and after six months of treatment with memantine, and found that the group receiving it had greater DMN connectivity in the precuneus than the placebo-treated group [16,39]. Other evidence suggests that donepezil treatment is associated with increased functional connectivity in the DMN (including the posterior cingulate cortex and the medial frontal gyrus) [16,40,41].

Understanding of a role for the DMN in AD progression, clinical outcomes, and treatment benefit is increasing. Future studies are needed to utilize these findings in the early detection and prevention of progression of the disease, as well as the development of novel treatments.

PARKINSON'S DISEASE (PD)

Another neurodegenerative and potentially neurocognitive condition, PD, has also been associated with dysfunction in the DMN. PD is characterized by neuronal damage and depigmentation of dopaminergic neurons in the substantia *nigra pars compacta*, which affects dopaminergic transmission. Clinically, PD is associated with impairments in the ability to regulate movement, producing the hallmark pathophysiological findings of bradykinesia, akinesia, masked facies, and generalized skeletal muscular rigidity [42]. With RS-fMRI, it is possible to measure disruption in the nigrostriatal dopamine system [43,44]. Striatal neurons have

been shown to coordinate activity not only in the basal ganglia, but also in cortical regions, specifically those in the DMN [45]. Evidence suggests that decreased functional connectivity in the DMN may play a role in the development of PD [46-50].

In patients with PD, decreased functional connectivity between areas of the DMN in resting state [49], as well as during cognitively demanding tasks [51], have been reported. Disease-related network disruptions have also been suggested to influence the functional coupling between the DMN and the central executive network (CEN), which includes the dorsolateral prefrontal cortex and the parietal cortex, and has been implicated in cognitive functions including reasoning, attention, inhibition, and working memory. These disrupted interactions may increase activation and dysfunctional connectivity of the DMN in individuals with PD [46].

In the healthy brain, the DMN and CEN are anti-correlated [52-54]. By contrast, those with PD display an altered pattern of network interactions, with positive coupling between the right CEN and the DMN [52,54]. Similar patterns of dysfunctional DMN large-scale connectivity have been identified in other disorders related to dopaminergic function, including schizophrenia [46,55]. Interestingly, several studies have demonstrated that increased connectivity within the DMN of PD is related to visual hallucinations [56,57], implying a specific role of the DMN related to the pathophysiology of this debilitating symptom.

Few studies have investigated DMN changes while assessing the effect of treatment in PD. One randomized, controlled crossover study provided levodopa to PD patients, and found that DMN dysfunction improved concurrently with improvements in motor symptoms, suggesting dopaminergic modulation in the DMN may underlie treatment effects in PD [58]. However, the subject number was limited (14 patients with PD and 13 healthy volunteers) and further studies of the effects of PD treatment on the DMN are needed.

EPILEPSY (TEMPORAL LOBE EPILEPSY)

Epilepsy is another neurological condition whose diagnosis and treatment could potentially benefit from analysis of the DMN because it involves dysregulated depolarization of specific neuronal networks [59-61]. One subtype of epilepsy, Temporal Lobe Epilepsy (TLE), has been most extensively investigated in relation to the DMN. In patients with TLE, the amplitude of the BOLD signal is increased in the mesial temporal lobe, but decreased in the DMN during interictal discharges (periods between seizure episodes) [61-63]. In addition, disruptions of functional connectivity between the mesial temporal lobe and the DMN have been reported [61,64-69]. These disruptions of functional connectivity in the DMN may contribute to the cognitive and/or psychiatric impairments associated with TLE [61].

For example, subjects with TLE had less antero-grade connectivity (from the anterior DMN to the posterior DMN) and retrograde connectivity (from the posterior DMN to the anterior DMN) when compared to healthy controls [13]. Subjects with left TLE had decreased connectivity of the posterior DMN with the hippocampus, parahippocampus, brainstem, and medial occipital cortex [13], whereas subjects with right TLE had areas of increased connectivity between the posterior and anterior DMN in the left lateral temporal cortex, precuneus, cingulum, and supplementary motor cortex [13], which was thought to be a compensatory mechanism [13].

Regarding changes in the DMN connectivity and their relationship to interictal epileptic discharges (IEDs) in TLE and idiopathic generalized epilepsy (IGE), baseline DMN connectivity has been reported as decreased in the hemisphere ipsilateral to the epileptic focus in TLE, whereas connectivity was more diffuse in IGE. Also, in both TLE and IGE, DMN connectivity has been found to be increased overall prior to the onset of an IED, but that post-IED, DMN connectivity increased significantly in the posterior cingulate only in the TLE group [14].

Although there is a dearth of information about treatment effects on DMN in TLE, one recent study suggested that altered connectivity in the DMN in TLE may be related to GABAergic and glutamatergic dysfunction [70]. In light of implications for the DMN in TLE pathophysiology, this finding may direct future studies evaluating potential TLE treatments.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

ADHD is characterized by developmentally inappropriate levels of hyperactivity, impulsivity, and inattention not otherwise attributable to other medical or psychiatric conditions, leading to significant functional impairment in multiple settings [27]. A clinical diagnosis, ADHD symptoms can sometimes be difficult to differentiate from childhood misbehavior or from the effect of other biological or psychosocial factors; brain imaging may detect structural and functional abnormalities and facilitate diagnosis [71].

One major cognitive deficit in ADHD is response inhibition, where an affected individual struggles to actively suppress an ongoing, inappropriate response [72]. To successfully perform a task, the DMN must be actively suppressed. Compared to healthy controls, subjects with ADHD have demonstrated stronger connections among DMN nodes than within the relevant nodes of the response inhibition network (including inferior frontal cortical, striatal, and thalamic areas) [73]. This DMN activation is thought to contribute to decreased task performance in ADHD [73,74]. In addition, interaction between the DMN and the cognitive

control network may be important in ADHD pathophysiology [75]. The cognitive control network (including the dorsal anterior cingulate cortex, supplementary motor area, dorsolateral prefrontal cortex, inferior frontal junction, anterior insular cortex, and posterior parietal cortex) is engaged when demanding cognitive processes such as working memory, inhibitory control, or set shifting occur [75,76].

Thus, the DMN and the cognitive control network function in opposing directions in relation to attentional demands — as attentional demands increase, activation of the cognitive control network increases, while DMN activation is attenuated. Conversely, during periods of rest, activation in the cognitive control network is decreased, and DMN activation increases [2,52,75].

Inverse control (suppression of the DMN by areas of the cognitive control network, including the dorsal anterior cingulate cortex, inferior frontal gyrus, and medial frontal gyrus) has frequently been shown to be weaker in ADHD patients than healthy controls, especially between the dorsal anterior cingulate cortex and the precuneus/posterior cingulate cortex. This suggests a disruption in the normal negative/inverse relationship between the cognitive control network and the DMN [20,75,77-79].

The putamen, a portion of the dorsal striatum involved in motor function and learning, has been of interest and used as a seed. Several studies have found negative connectivity between the putamen and the DMN in healthy children, which was shown to be attenuated in children with ADHD [73,77]. These results contrast with findings indicating connectivity between the cognitive control network and the DMN, but additional evidence suggests that interference from the DMN may impair normal attentional functioning in ADHD [75,80].

Thus, the DMN appears to be involved in the pathophysiology of ADHD, and the importance of the disrupted connectivity between the cognitive control network and the DMN suggests a neurocognitive model for ADHD. The DMN has been studied to assess treatment effects in ADHD. For example, methylphenidate normalized the increased threshold of salient stimuli to deactivate the DMN when performing a task requiring response-inhibition [74]. Atomoxetine treatment also normalized connectivity between the cognitive control network and the DMN in patients with ADHD [81].

Understanding of the DMN's role in ADHD pathophysiology is growing, specifically the neurocognitive model incorporating connectivity between the cognitive control network and the DMN. Further study of this connection has potential to aid in the phenotyping of ADHD, advance understanding of the neurobiological mechanisms of ADHD, and improve understanding of the effects of treatments. Future studies investigating the DMN's role in the pathophysiology of ADHD, along with studies of treatment effects, are indicated.

MOOD DISORDERS (MAJOR DEPRESSIVE DISORDER AND BIPOLAR DISORDER)

Cognitive symptoms, including difficulty with concentration/focus, executive function disturbances, and symptoms such as rumination are common features of mood disorders [10,27]. Evidence suggests that abnormal DMN function is associated with these symptoms, particularly rumination [10,82,83]. Decreased functional connectivity between the posterior cingulate cortex and the precuneus, and increased DMN dominance over the task-positive network activity, have been associated with higher levels of rumination, involving the repetition of thoughts and ideas, in depressed subjects [82-84]. Additionally, hyperconnectivity of the subgenual cingulate cortex with the posterior cingulate cortex has been reported in major depressive disorder (MDD) with depressive rumination [85]. This may be related to the function of the subgenual anterior cingulate cortex, which is implicated in channeling emotional influences from the limbic circuitry to prefrontal cortical areas. Thus, activation of the DMN by the subgenual-cingulate in patients with depression related to this hyperconnectivity could contribute to rumination [10]. This may relate to the reported correlation between the duration of a major depressive episode and the altered connectivity among the subgenual anterior cingulate cortex and the DMN [10,86].

Fewer studies have examined the DMN in patients with bipolar disorder (BD). Yet, higher levels of coherence between the left parietal cortex, left fusiform gyrus, right visual and auditory association cortex, and left frontal polar cortex have been found in subjects with BD than in healthy controls [55]. These studies also reported a correlation of connectivity among the medial parietal cortex, parahippocampal gyrus, and DMN with Young Mania Rating Scale scores [55,87]. Another study found differences in regional homogeneity (defined by the similarity of the BOLD signal intensity time series among the voxels in the region) within the DMN of depressed subjects with BD compared to healthy controls. More specifically, BD was associated with increased regional homogeneity in the medial frontal gyrus and inferior parietal lobe. This also correlated with the number of depressive episodes [88].

Although limited data are available regarding treatment effects on the DMN in patients with mood disorders, one recent study demonstrated a normalization of DMN function in 30 percent of the patients with MDD after receiving antidepressant treatment [89]. In conclusion, the DMN appears to be affected in mood disorders, and may be related to rumination. Further investigations of these relationships and treatment effects are underway and additional studies are required to refine biological models for mood disorders.

Table 1. Summary of DMN findings in neurological and neuropsychiatric conditions.

Alzheimer's disease (AD)		
Major Findings	Effects of Treatment	Future Directions
1. Decreased functional connectivity between posterior and anterior portions of the DMN [28-31]	Increased DMN connectivity after memantine and donepezil treatment [16,40,41]	Early detection, development of novel targeted treatments using DMN assessments
2. Overlap between the DMN and patterns of amyloid deposits [16,37,38]		
Parkinson's disease (PD)		
Major Findings	Effects of Treatment	Future Directions
1. Coordinated activity of striatum and the DMN [45]	Normalization of DMN function after administration of levodopa [58]	Early detection, development of novel targeted treatments using DMN assessments
2. Network disruptions in the DMN and CEN — heightened activation and dysfunctional connectivity [46]		
3. Visual hallucination-related increased DMN connectivity [56,57]		
Temporal Lobe Epilepsy (TLE)		
Major Findings	Effects of Treatment	Future Directions
1. Disrupted functional connectivity between the mesial temporal lobe and DMN regions, related to cognitive and psychiatric impairments [61,64-69]	Potential relationship between GABAergic and glutamatergic dysfunction and altered DMN connectivity [70]	Potential role of DMN assessment in treatment development
2. Distinct patterns of the DMN connectivity depending on the laterality of TLE [13]		
3. Variations in DMN connectivity depending on seizure phase [14]		
Attention deficit hyperactivity disorder (ADHD)		
Major Findings	Effects of Treatment	Future Directions
1. Correlation between maintained DMN activation and impaired task performance [73,74]	Normalization of disrupted connectivity between the cognitive control network and the DMN after treatment with atomoxetine and methylphenidate [74,81]	Studies of treatment effects and bio-typing
2. Attenuated negative connectivity between the cognitive control network and the DMN [20,75,77-79]		
3. Attenuated negative connectivity between the putamen and the DMN [75,80]		
Mood Disorders		
Major Findings	Effects of Treatment	Future Directions
1. Dysfunctional connectivity in the DMN and its relation to symptoms (especially rumination) [82-85,88]	Normalization of DMN function after antidepressant medication treatment in MDD [89]	Relationships between symptoms or dimensions in mood disorders and DMN function along with treatment effects
2. Correlation between the duration and number of the depressive episodes and disrupted DMN connectivity [10,86]		

DISCUSSION

The clinical implications of the DMN in neurological and neuropsychiatric disorders have been, and continue to be, targets of investigation. In disorders including AD, PD, TLE, ADHD, and mood disorders, the DMN has been implicated in neurobiological/neurocognitive pathophysiological models [10,28,49,61,75]. A few studies have investigated the possibility of DMN assessment for early detection [28,29] and treatment efficacy [39,58,74,89]. Intrinsic DMN connectivity patterns, as well as those between the DMN and other neural networks, are of particular interest for developing neurocognitive models. Disrupted connectivity within the DMN has been frequently reported, particularly between the anterior (anterior cingulate cortex and medial prefrontal cortex) and posterior portions (precuneus and posterior cingulate cortex) [28-31].

Additional studies have examined functional connectivity between the DMN and other networks, such as the CEN [52-54] and the cognitive control network [75,76]. For example, depressed subjects showed increased connectivity between subgenual-cingulate cortex and posterior cingulate cortex, which was related to rumination [10,82,83]. In ADHD, symptoms may be related to attenuated negative connectivity between the cognitive control network and the DMN [75,80]. In PD, network alterations may influence the functional coupling between the DMN and the CEN [46]. Decreased functional connectivity in the DMN has been noted in AD, particularly between the posterior (precuneus, posterior cingulate cortex) and anterior portions (anterior cingulate cortex and medial prefrontal cortex) [28-31]. In left TLE, decreased connectivity of the posterior DMN with the hippocampus, parahippocampus, brainstem, and medial occipital cortex has been found [13]. In contrast, right TLE has been associated with increased connectivity between the posterior and anterior DMN in the left lateral temporal cortex, precuneus, cingulum, and supplementary motor cortex [13].

Despite intriguing evidence, several limitations exist regarding the interpretation of DMN findings in neurological and neuropsychiatric disorders. Unfortunately, many of the changes are non-specific and overlapping, challenging the development of disease-specific biological models. Also, it is difficult to interpret disrupted DMN activity without relying on task-related neural activation, so most studies instead include task-related data [21,22]. Additionally, movement and physiological confounding factors are difficult to limit in certain populations, particularly PD and ADHD [90].

Finally, and perhaps most fundamentally, the applicability of using resting state as a reference condition to compare with patterns of activation involving task conditions has been questioned [91]. Importantly, activity during “resting state” may not adequately distinguish this state from other engaged states for task perform-

ance [91]. Despite these limitations, investigations of the DMN in neurological and neuropsychiatric conditions may provide insight into pathophysiology as well as aid in diagnosis and prediction. These studies provide evidence supporting neurobiological models and can help direct future studies. Such research is critical to deepen understanding and identify novel treatments.

CONCLUSION

Despite some limitations, research on the DMN has helped support biological models and understand treatment efficacy. Future studies with increased subject numbers and refined techniques can potentially facilitate early detection of neurological and neuropsychiatric conditions, subtype definition, and the development of neurobiologically-targeted novel treatments.

Conflict of interest: Akansha Mohan, Aaron J. Roberto, Abhishek Mohan, Aileen Lorenzo, Kathryn Jones, Luis Liogier-Weyback, Martin J. Carney and Soonjo Hwang have no financial support or other disclosures. Kyle A.B. Lapidus has received research support from the Brain and Behavior Research Foundation, Le Foundation, Education and Research Foundation for Nuclear Medicine and Molecular Imaging, and Simons Foundation. He serves on the advisory board for Halo Neuroscience, has received devices, meals, travel and research support from Medtronic, Halo Neuroscience, and Brainsway, has consulted for FCB Health, and consults for LCN Consulting Inc. None of these directly overlap with the content of this manuscript.

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