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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

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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.

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REFERENCES

1. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci.* 2008;1124:1-38.
2. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proc Natl Acad Sci U S A.* 2001;98(2):676-82.
3. Raichle ME. The brain's default mode network. *Annu Rev Neurosci.* 2015;38:433-47.
4. Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJ. Default-mode brain dysfunction in mental disorders: a systematic review. *Neurosci Biobehav Rev.* 2009;33(3):279-96.
5. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci.* 2007;8(9):700-11.
6. Huettel SA, Song AW, McCarthy G. *Functional Magnetic Resonance Imaging.* 2nd ed. Massachusetts: Sinauer; 2009.
7. Lee MH, Smyser CD, Shimony JS. Resting-state fMRI: a review of methods and clinical applications. *AJNR Am J Neuroradiol.* 2013;34(10):1866-72.
8. Rosazza C, Minati L, Ghielmetti F, Mandelli ML, Bruzzone MG. Functional connectivity during resting-state functional MR imaging: study of the correspondence between independent component analysis and region-of-interest-based methods. *AJNR Am J Neuroradiol.* 2012;33(1):180-7.
9. Buckner RL. The serendipitous discovery of the brain's default network. *Neuroimage.* 2012;62(2):1137-45.
10. Cha DS, De Michele F, Soczynska JK, Woldeyohannes HO, Kaidanovich-Beilin O, Carvalho AF, et al. The putative impact of metabolic health on default mode network activity and functional connectivity in neuropsychiatric disorders. *CNS Neurol Disord Drug Targets.* 2014;13(10):1750-8.

11. Sala-Llonch R, Bartrés-Faz D, Junqué C. Reorganization of brain networks in aging: a review of functional connectivity studies. *Front Psychol.* 2015;6:663.
12. Franzen JD, Heinrichs-Graham E, White ML, Wetzel MW, Knott NL, Wilson TW. Atypical coupling between posterior regions of the default mode network in attention-deficit/hyperactivity disorder: a pharmaco-magnetoencephalography study. *J Psychiatry Neurosci.* 2013;38(5):333-40.
13. Haneef Z, Lenartowicz A, Yeh HJ, Engel J Jr, Stern JM. Network analysis of the default mode network using functional connectivity MRI in Temporal Lobe Epilepsy. *J Vis Exp.* 2014;(90):e51442.
14. Lopes R, Moeller F, Besson P, Ogez F, Szurhaj W, Leclerc X, et al. Study on the Relationships between Intrinsic Functional Connectivity of the Default Mode Network and Transient Epileptic Activity. *Front Neurol.* 2014;5:201.
15. Shi H, Wang X, Yi J, Zhu X, Zhang X, Yang J, et al. Default mode network alterations during implicit emotional faces processing in first-episode, treatment-naive major depression patients. *Front Psychol.* 2015;6:1198.
16. Dennis EL, Thompson PM. Functional brain connectivity using fMRI in aging and Alzheimer's disease. *Neuropsychol Rev.* 2014;24(1):49-62.
17. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A.* 2003;100(1):253-8.
18. Greicius MD, Menon V. Default-mode activity during a passive sensory task: uncoupled from deactivation but impacting activation. *J Cogn Neurosci.* 2004;16(9):1484-92.
19. Buckner RL, Snyder AZ, Shannon BJ, LaRossa G, Sachs R, Fotenos AF, et al. Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. *J Neurosci.* 2005;25(34):7709-17.
20. Castellanos FX, Margulies DS, Kelly C, Uddin LQ, Ghafari M, Kirsch A, et al. Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. *Biol Psychiatry.* 2008;63(3):332-7.
21. Uddin LQ, Kelly AM, Biswal BB, Margulies DS, Shehzad Z, Shaw D. Network homogeneity reveals decreased integrity of default-mode network in ADHD. *J Neurosci Methods.* 2008;169(1):249-54.
22. Maddock RJ. The retrosplenial cortex and emotion: new insights from functional neuroimaging of the human brain. *Trends Neurosci.* 1999;22(7):310-6.
23. Gusnard DA, Akbudak E, Shulman GL, Raichle ME. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc Natl Acad Sci U S A.* 2001;98(7):4259-64.
24. Simpson JR Jr, Snyder AZ, Gusnard DA, Raichle ME. Emotion-induced changes in human medial prefrontal cortex: I. During cognitive task performance. *Proc Natl Acad Sci U S A.* 2001;98(2):683-7.
25. Braak H, Braak E. Staging of Alzheimer-related cortical destruction. *Int Psychogeriatr.* 1997;9(Suppl 1):257-61; discussion 269-72.
26. Delacourte A, David JP, Sergeant N, Buée L, Watzel A, Vermeersch P, et al. The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. *Neurology.* 1999;52(6):1158-65.
27. American Psychiatric Association. *Diagnostic and Statistical Manual 5.* Washington (DC): American Psychiatric Association; 2013.
28. Gili T, Cercignani M, Serra L, Perri R, Giove F, Maraviglia B, et al. Regional brain atrophy and functional disconnection across Alzheimer's disease evolution. *J Neurol Neurosurg Psychiatry.* 2011;82(1):58-66.
29. Griffanti L, Dipasquale O, Laganà MM, Nemni R, Clerici M, Smith SM, et al. Effective artifact removal in resting state fMRI data improves detection of DMN functional connectivity alteration in Alzheimer's disease. *Front Hum Neurosci.* 2015;9:449.
30. Brier MR, Thomas JB, Snyder AZ, Benzinger TL, Zhang D, Raichle ME, et al. Loss of intranetwork and internetwork resting state functional connections with Alzheimer's disease progression. *J Neurosci.* 2012;32(26):8890-9.
31. Hafkemeijer A, van der Grond J, Rombouts SA. Imaging the default mode network in aging and dementia. *Biochim Biophys Acta.* 2012;1822(3):431-41.
32. Filippini N, MacIntosh BJ, Hough MG, Goodwin GM, Frisoni GB, Smith SM, et al. Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. *Proc Natl Acad Sci U S A.* 2009;106(17):7209-14.
33. Sorg C, Riedl V, Pernecky R, Kurz A, Wohlschläger AM. Impact of Alzheimer's disease on the functional connectivity of spontaneous brain activity. *Curr Alzheimer Res.* 2009;6(6):541-53.
34. Cha J, Jo HJ, Kim HJ, Seo SW, Kim HS, Yoon U, et al. Functional alteration patterns of default mode networks: comparisons of normal aging, amnesic mild cognitive impairment and Alzheimer's disease. *Eur J Neurosci.* 2013;37(12):1916-24.
35. Wang L, Li H, Liang Y, Zhang J, Li X, Shu N, et al. Amnesic mild cognitive impairment: topological reorganization of the default-mode network. *Radiology.* 2013;268(2):501-14.
36. Li X, Cao M, Zhang J, Chen K, Chen Y, Ma C, et al. Structural and functional brain changes in the default mode network in subtypes of amnesic mild cognitive impairment. *J Geriatr Psychiatry Neurol.* 2014;27(3):188-98.
37. Hedden T, Van Dijk KR, Becker JA, Mehta A, Sperling RA, Johnson KA, et al. Disruption of functional connectivity in clinically normal older adults harboring amyloid burden. *J Neurosci.* 2009;29(40):12686-94.
38. Mormino EC, Smiljic A, Hayenga AO, Onami SH, Greicius MD, Rabinovici GD, et al. Relationships between beta-amyloid and functional connectivity in different components of the default mode network in aging. *Cereb Cortex.* 2011;21(10):2399-407.
39. Lorenzi M, Beltramello A, Mercuri NB, Canu E, Zoccatelli G, Pizzini FB, et al. Effect of memantine on resting state default mode network activity in Alzheimer's disease. *Drugs Aging.* 2011;28(3):205-17.
40. Goveas JS, Xie C, Ward BD, Wu Z, Li W, Franczak M. Recovery of hippocampal network connectivity correlates with cognitive improvement in mild Alzheimer's disease patients treated with donepezil assessed by resting-state fMRI. *J Magn Reson Imaging.* 2011;34(4):764-73.
41. Li W, Antuono PG, Xie C, Chen G, Jones JL, Ward BD, et al. Changes in regional cerebral blood flow and functional connectivity in the cholinergic pathway associated with cognitive performance in subjects with mild Alzheimer's disease after 12-week donepezil treatment. *Neuroimage.* 2012;60(2):1083-91.
42. de Rijk MC, Tzourio C, Breteler MM, Dartigues JF, Amaducci L, Lopez-Pousa S, et al. Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON Collaborative Study. European Community Concerted Action on the Epidemiology of Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 1997;62(1):10-15.
43. Tahmasian M, Bettray LM, van Eimeren T, Drzezga A, Timmermann L, Eickhoff CR, et al. A systematic review on the applications of resting-state fMRI in Parkinson's disease: Does dopamine replacement therapy play a role? *Cortex.* 2015;73:80-105.
44. Müller-Oehring EM, Sullivan EV, Pfefferbaum A, Huang NC, Poston KL, Bronte-Stewart HM, et al. Task-rest modulation of basal ganglia connectivity in mild to moderate Parkinson's disease. *Brain Imaging Behav.* 2015;9(3):619-38.

45. Kwak Y, Peltier S, Bohnen NI, Müller ML, Dayalu P, Seidler RD. Altered resting state cortico-striatal connectivity in mild to moderate stage Parkinson's disease. *Front Syst Neurosci*. 2010;4:143.
46. Putcha D, Ross RS, Cronin-Golomb A, Janes AC, Stern CE. Altered intrinsic functional coupling between core neurocognitive networks in Parkinson's disease. *Neuroimage Clin*. 2015;7:449-55.
47. Disbrow EA, Carmichael O, He J, Lanni KE, Dressler EM, Zhang L, et al. Resting state functional connectivity is associated with cognitive dysfunction in non-demented people with Parkinson's disease. *J Parkinsons Dis*. 2014;4(3):453-65.
48. Rektorova L. Resting-state networks in Alzheimer's disease and Parkinson's disease. *Neurodegener Dis*. 2014;13(2-3):186-8.
49. Tessitore A, Esposito F, Vitale C, Santangelo G, Amboni M, Russo A. Default-mode network connectivity in cognitively unimpaired patients with Parkinson disease. *Neurology*. 2012;79(23):2226-32.
50. Krajcovicova L, Mikl M, Marecek R, Rektorova I. The default mode network integrity in patients with Parkinson's disease is levodopa equivalent dose-dependent. *J Neural Transm (Vienna)*. 2012;119(4):443-54.
51. van Eimeren T, Monchi O, Ballanger B, Strafella AP. Dysfunction of the default mode network in Parkinson disease: a functional magnetic resonance imaging study. *Arch Neurol*. 2009;66(7):877-83.
52. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci U S A*. 2005;102(27):9673-8.
53. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn Sci*. 2011;15(10):483-506.
54. Sridharan D, Levitin DJ, Menon V. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proc Natl Acad Sci U S A*. 2008;105(34):12569-74.
55. Ongür D, Lundy M, Greenhouse I, Shinn AK, Menon V, Cohen BM, et al. Default mode network abnormalities in bipolar disorder and schizophrenia. *Psychiatry Res*. 2010;183(1):59-68.
56. Franciotti R, Delli Pizzi S, Perfetti B, Tartaro A, Bonanni L, Thomas A, et al. Default mode network links to visual hallucinations: A comparison between Parkinson's disease and multiple system atrophy. *Mov Disord*. 2015;30(9):1237-47.
57. Yao N, Shek-Kwan Chang R, Cheung C, Pang S, Lau KK, Suckling J, et al. The default mode network is disrupted in Parkinson's disease with visual hallucinations. *Hum Brain Mapp*. 2014;35(11):5658-66.
58. Delaveau P, Salgado-Pineda P, Fossati P, Witjas T, Azulay JP, Blin O. Dopaminergic modulation of the default mode network in Parkinson's disease. *Eur Neuropsychopharmacol*. 2010;20(11):784-92.
59. Helmstaedter C. Effects of chronic epilepsy on declarative memory systems. *Prog Brain Res*. 2002;135:439-53.
60. Oyegbile TO, Dow C, Jones J, Bell B, Rutecki P, Sheth R, et al. The nature and course of neuropsychological morbidity in chronic temporal lobe epilepsy. *Neurology*. 2004;62(10):1736-42.
61. Hsiao FJ, Yu HY, Chen WT, Kwan SY, Chen C, Yen DJ, et al. Increased Intrinsic Connectivity of the Default Mode Network in Temporal Lobe Epilepsy: Evidence from Resting-State MEG Recordings. *PLoS One*. 2015;10(6):e0128787.
62. Zhang Z, Lu G, Zhong Y, Tan Q, Chen H, Liao W, et al. fMRI study of mesial temporal lobe epilepsy using amplitude of low-frequency fluctuation analysis. *Hum Brain Mapp*. 2010;31(12):1851-61.
63. Laufs H, Hamandi K, Salek-Haddadi A, Kleinschmidt AK, Duncan JS, Lemieux L. Temporal lobe interictal epileptic discharges affect cerebral activity in "default mode" brain regions. *Hum Brain Mapp*. 2007;28(10):1023-32.
64. Pittau F, Grova C, Moeller F, Dubeau F, Gotman J. Patterns of altered functional connectivity in mesial temporal lobe epilepsy. *Epilepsia*. 2012;53(6):1013-23.
65. Morgan VL, Sonmez Turk HH, Gore JC, Abou-Khalil B. Lateralization of temporal lobe epilepsy using resting functional magnetic resonance imaging connectivity of hippocampal networks. *Epilepsia*. 2012;53(9):1628-35.
66. Voets NL, Beckmann CF, Cole DM, Hong S, Bernasconi A, Bernasconi N. Structural substrates for resting network disruption in temporal lobe epilepsy. *Brain*. 2012;135(8):2350-7.
67. Liao W, Zhang Z, Pan Z, Mantini D, Ding J, Duan X, et al. Altered functional connectivity and small-world in mesial temporal lobe epilepsy. *PLoS One*. 2010;5(1):e8525.
68. Pereira FR, Alessio A, Sercheli MS, Pedro T, Bilevicius E, Rondina JM, et al. Asymmetrical hippocampal connectivity in mesial temporal lobe epilepsy: evidence from resting state fMRI. *BMC Neurosci*. 2010;11:66.
69. Bettus G, Bartolomei F, Confort-Gouny S, Guedj E, Chauvel P, Cozzone PJ, et al. Role of resting state functional connectivity MRI in presurgical investigation of mesial temporal lobe epilepsy. *J Neurol Neurosurg Psychiatry*. 2010;81(10):1147-54.
70. Nugent AC, Martinez A, D'Alfonso A, Zarate CA, Theodore WH. The relationship between glucose metabolism, resting-state fMRI BOLD signal, and GABAA-binding potential: a preliminary study in healthy subjects and those with temporal lobe epilepsy. *J Cereb Blood Flow Metab*. 2015;35(4):583-91.
71. Bradstreet JJ, Smith S, Baral M, Rossignol DA. Biomarker-guided interventions of clinically relevant conditions associated with autism spectrum disorders and attention deficit hyperactivity disorder. *Altern Med Rev*. 2010;15(1):15-32.
72. dos Santos Siqueira A, Biazoli Junior CE, Comfort WE, Rohde LA, Sato JR, et al. Abnormal functional resting-state networks in ADHD: graph theory and pattern recognition analysis of fMRI data. *Biomed Res Int*. 2014;2014:380531.
73. van Rooij D, Hartman CA, Mennes M, Oosterlaan J, Franke B, Rommelse N, et al. Altered neural connectivity during response inhibition in adolescents with attention-deficit/hyperactivity disorder and their unaffected siblings. *Neuroimage Clin*. 2015;7:325-35.
74. Liddle EB, Hollis C, Batty MJ, Groom MJ, Totman JJ, Liotti M. Task-related default mode network modulation and inhibitory control in ADHD: effects of motivation and methylphenidate. *J Child Psychol Psychiatry*. 2011;52(7):761-71.
75. Posner J, Park C, Wang Z. Connecting the dots: a review of resting connectivity MRI studies in attention-deficit/hyperactivity disorder. *Neuropsychol Rev*. 2014;24(1):3-15.
76. Cole MW, Schneider W. The cognitive control network: Integrated cortical regions with dissociable functions. *Neuroimage*. 2007;37(1):343-60.
77. Sun L, Cao Q, Long X, Sui M, Cao X, Zhu C, et al. Abnormal functional connectivity between the anterior cingulate and the default mode network in drug-naive boys with attention deficit hyperactivity disorder. *Psychiatry Res*. 2012;201(2):120-7.
78. Sato JR, Hoexter MQ, Castellanos XF, Rohde LA. Abnormal brain connectivity patterns in adults with ADHD: a coherence study. *PLoS One*. 2012;7(9):e45671.
79. Hoekzema E, Carmona S, Ramos-Quiroga JA, Richarte Fernández V, Bosch R, Soliva JC, et al. An independent components and functional connectivity analysis of resting state fMRI data points to neural network dysregulation in adult ADHD. *Hum Brain Mapp*. 2014;35(4):1261-72.
80. Cao X, Cao Q, Long X, Sun L, Sui M, Zhu C, et al. Abnormal resting-state functional connectivity patterns of the putamen in medication-naive children with attention deficit hyperactivity disorder. *Brain Res*. 2009;1303:195-206.
81. Lin HY, Gau SS. Atomoxetine Treatment Strengthens an Anti-Correlated Relationship between Functional Brain Net-

- works in Medication-Naive Adults with Attention-Deficit Hyperactivity Disorder: A Randomized Double-Blind Placebo-Controlled Clinical Trial. *Int J Neuropsychopharmacol.* 2015;pii:pyy094.
82. Zhu X, Wang X, Xiao J, Liao J, Zhong M, Wang W, et al. Evidence of a dissociation pattern in resting-state default mode network connectivity in first-episode, treatment-naive major depression patients. *Biol Psychiatry.* 2012;71(7):611-7.
 83. Guo W, Liu F, Xue Z, Gao K, Liu Z, Xiao C, et al. Decreased interhemispheric coordination in treatment-resistant depression: a resting-state fMRI study. *PLoS One.* 2013;8(8):e71368.
 84. Hamilton JP, Furman DJ, Chang C, Thomason ME, Dennis E, Gotlib IH. Default-mode and task-positive network activity in major depressive disorder: implications for adaptive and maladaptive rumination. *Biol Psychiatry.* 2011;70(4):327-33.
 85. Berman MG, Peltier S, Nee DE, Kross E, Deldin PJ, Jonides J. Depression, rumination and the default network. *Soc Cogn Affect Neurosci.* 2011;6(5):548-55.
 86. Sheline YI, Price JL, Yan Z, Mintun MA. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. *Proc Natl Acad Sci U S A.* 2010;107(24):11020-25.
 87. Vargas C, López-Jaramillo C, Vieta E. A systematic literature review of resting state network — functional MRI in bipolar disorder. *J Affect Disord.* 2013;150(3):727-35.
 88. Liu CH, Ma X, Li F, Wang YJ, Tie CL, Li SF, et al. Regional homogeneity within the default mode network in bipolar depression: a resting-state functional magnetic resonance imaging study. *PLoS One.* 2012;7(11):e48181.
 89. Qin J, Shen H, Zeng LL, Jiang W, Liu L, Hu D. Predicting clinical responses in major depression using intrinsic functional connectivity. *Neuroreport.* 2015;26(12):675-80.
 90. Power JD, Mitra A, Laumann TO, Snyder AZ, Schlaggar BL, Petersen SE. Methods to detect, characterize, and remove motion artifact in resting state fMRI. *Neuroimage.* 2014;84:320-41.
 91. Morcom AM, Fletcher PC. Does the brain have a baseline? Why we should be resisting a rest. *Neuroimage.* 2007;37(4):1073-82.