Default mode network anti-correlation as a transdiagnostic biomarker of cognitive function

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Conflict of interest

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Abstract

The default mode network (DMN) is intricately linked with processes such as self-referential thinking, episodic memory recall, self-projection, and understanding the mindset of others. Over recent years, there has been a surge in examining its functional connectivity, particularly its antagonistic relationship with frontoparietal networks (FPN) involved in top-down attention, executive function, and cognitive control. Notably, the DMN demonstrates an anti-correlated connection with FPN and Dorsal Attention Network (DAN), leading to its deactivation when one's attention is turned towards the external environment. The fluidity in switching between these internal and external modes of processing—highlighted by this anti-correlated functional connectivity—has been proposed as an indicator of cognitive health and mediated by salience networks (SAL). Due to the ease of the estimation of functional connectivity-based measures through resting state fMRI paradigms, there is now a wealth of large-scale datasets, paving the way for standardized connectivity benchmarks. This review delves into the promising role of DMN connectivity metrics as potential biomarkers of cognitive state across attention, mind wandering and meditation states, and investigating deviations in clinical conditions such as anxiety, depression, ADHD, PTSD and others. Additionally, we tackle the issue of reliability of network estimation and functional connectivity and share recommendations for using connectivity measures as a biomarker of cognitive health.

Introduction

The default mode network (DMN) is a macroscale brain network associated with higher-order and internally-oriented cognitive processes including episodic projection, theory of mind (TOM), and autobiographical processing (1). Its constituent regions span the posterior cingulate cortex (PCC), medial prefrontal cortex (mPFC), temporo-parietal junction (TPJ), angular gyrus, inferior parietal lobule (IPL) and along the temporal cortex (2–4). The DMN can be decomposed into multiple subnetworks (5,6) where the first subnetwork is associated with episodic projection (thinking about the past or the future) and another with thinking about others/TOM (7,8). Studies also suggest the presence of another subnetwork anchored along the medial temporal lobe which is linked with mind wandering and spontaneous thought (9,10). DMN activity is highly task- and context-dependent and changes across days and scanning sessions (11,12). Recently, the use of precision imaging, where subjects are scanned across multiple sessions, has illustrated the variability of DMN and other higher order cognitive networks across individuals (13–15) suggesting that averaged atlases may lose a lot of individual specific variations and may result in less reliable network estimations (16,17).

The relationship between the DMN and other large scale brain networks is of growing interest to the neuroimaging community. While inconsistencies surrounding network nomenclature hamper progress in this area (18,19), reproducible findings suggest the DMN frequently interacts with multiple other networks. The frontoparietal networks (FPN), also known as the cognitive control network (CCN) or Central Executive Network (CEN), is anchored predominantly across the lateral prefrontal cortex, dorsal IPL, supplementary motor area and is involved in top down control processes like executive function and working memory. These regions often co-activate with the dorsal attention network (DAN) which is centered in the posterior parietal cortex (PPC) along with the frontal eye fields (FEF) in the PFC. The Salience Network (SAL) is involved in deploying attentional resources and usually associated with switching between internal and external attention (20). Recent precision imaging studies have found that higher order cognitive regions form supra areal association megaclusters (SAAMs) where DMN and FPN regions along with language regions are organized in clusters across the cortex, striatum and the cerebellum (14,21) highlighting a distributed processing architecture (22). Though traditionally considered exclusive to externally-oriented tasks and displaying an antagonistic relationship with DMN, the FPN is now understood to also support internally-oriented cognition as evidenced by its co-activation with the DMN during goal-directed thought (23,24).

Reports of antagonistic relationships between the DMN and lateral frontoparietal networks date back to the early 2000s. The first publication to report negative correlations between a node of the DMN (posterior cingulate cortex, PCC) and lateral prefrontal cortices was also the first to conduct a network analysis of the default mode hypothesis (3). Two studies published a few years later in 2005 provided further evidence of negative correlations (or anti-correlations) between the DMN and other frontoparietal large-scale brain networks (2,25). In both of these studies, the PCC was again used as a “seed” region-of-interest to reveal whole-brain patterns of functionally connected regions comprising the DMN. The authors of both studies posited the existence of a dynamic interplay between the internally-oriented DMN and externally-oriented systems for attention and cognitive control (see (18) for discussion of network nomenclature issues complicating precise identification of frontoparietal networks implicated). Studies since then have shown individual differences in this anti-correlated activity is associated with a wide array of behavioral variability (12,26,27).

In this review, we will highlight the literature on the DMN anti-correlated networks across attention and mind-wandering and explore how these anti-correlations are affected across various clinical conditions. We will examine how DMN connectivity is impacted by meditative practices and if it can be used as a stable biomarker of cognition and health. We conclude with guidelines and recommendations of how to estimate functional connectivity (FC) measures across these networks for future use in precision psychiatry.

DMN and attention/mind-wandering

Although attention is often considered an elusive construct because of its centrality in nearly all aspects of our waking lives (28), it is frequently defined as involving processes that select and prioritize representations most relevant to the task at hand, while filtering out task-irrelevant representations (29). Individual differences in the strength of anti-correlation between the DMN and FPN during attention task performance are correlated with response time variability. Greater network segregation, measured as stronger negative correlations between the DMN and FPN, is associated with less variable behavioral performance on a flanker attention task (26). These findings have since been directly replicated in a large population neuroscience dataset, where they have been further linked with attention problems (30).

Mind-wandering, a phenomenological construct, often considered to be antithetical to focused attention, involves the spontaneous shifting of this focused attention away from the external environment to inner thoughts (31,32). Seminal neuroimaging studies investigating attention and mind-wandering, traditionally linked activity in the FPN to supporting selective and sustained attention (33), and in contrast linked activity within the DMN to mind-wandering that was due to a failure of DMN suppression (33,34). Studies have used a rest condition where participants were instructed to do "nothing" to identify the DMN (1,4). During these rest periods, blood flow in midline cortical structures increased, suggesting the link between neuronal activity in DMN regions and spontaneous cognition or mind-wandering. Examining this link directly, Mason and colleagues (34) compared neural activations when participants performed practiced versus novel task sequences. Increases in automaticity were associated with a greater predilection for task-unrelated thoughts and less reduction in regions of the DMN compared to a novel task, highlighting the involvement of the network during tasks that result in greater off-task thinking. Furthermore, a meta-analytic review, synthesizing 24 neuroimaging investigations of mind-wandering, solidified the recognition of the key role played by the transmodal nodes of the DMN (specifically the PCC/precuneus, the mPFC, and the coupling between nodes of the DMN and FPN) in supporting the internal stream of thinking (35).

More recently, however, the application of connectomics, which prioritizes developing a comprehensive understanding of the role played by all canonical networks rather than just a select, apriori defined set of networks, has suggested that emergent constructs such as attention and mind-wandering are encoded by distributed, multi-region networks (36). In one such application, Rosenberg and colleagues used connectome-based predictive modeling (CPM) to derive a whole-brain signature of sustained attention. This neural signature, known as sustained attention CPM, spans multiple canonical networks beyond the frontoparietal and default mode networks, including the visual networks, the cerebellar network, and the motor network. Impressively, it predicted over 70% of the variance in a gradual continuous performance task in young adults (37). Significantly, this neural signature of sustained attention successfully predicted symptom severity in children with attention-deficit/hyperactivity disorder (37), behavioral metrics of attention on a stop signal task (38), attention network task (39), and Stroop task (40). In a related endeavor, Gbadeyan and colleagues, employing the CPM methodology, developed a whole-brain model of mind-wandering (41). The resulting model, comprising 268 functional connections, provided support for the differential involvement of the key canonical networks, including the DMN, the somatomotor network, the DAN, the ventral attention network, the visual network, and the FPN, in both high and low mind-wandering.

Collectively, while earlier studies on attention and mind-wandering supported the double dissociation of FPN and DMN in the seemingly opposing phenomena of attention and mind-wandering, more recent empirical support highlights the involvement of both these networks, along with other canonical networks, in supporting attention and mind-wandering.

DMN and meditation

Meditation refers to contemplative practices that involve regulating both body and mind through cultivating a state of heightened awareness (42) and includes a wide variety of techniques and approaches rooted in various traditions (43). Recent years have seen a surge of meditation and mindfulness-based interventions carried out either as therapeutic tools or interventions for the general public (44,45). Indeed, a large body of ongoing work converges on the positive effects of meditation, including enhanced emotion regulation, wellbeing and stress reduction (46–48), enhanced attentional skills (49,50), and alleviation of the symptoms of various mental conditions. Despite attempts to categorize diverse meditation styles (51–53), the neural correlates of meditation remain complex to describe simply, often exhibiting discrepancies across different styles (54,55).

Nevertheless, converging evidence based on study of various practices points toward the DMN as a key network whose activity and FC is modified both during the meditative state and as a trait following regular meditation practice (56,57). Numerous studies have demonstrated reduced activity in various nodes of the DMN during meditative states compared to rest (57–59) and also beyond the de-activation induced by task (60). Reduced DMN activity has also been shown during resting state of experienced meditators compared to controls (61,62). Furthermore, FC within the DMN is altered during and following meditation. Evidence for decreased FC between DMN nodes involved in mind-wandering and self-referential processes has been observed in experienced meditators compared to controls during meditation (58,59,63) and at rest (61,62,64). Conversely, evidence for increased within-DMN FC has been observed during meditation (61) and at rest, specifically in the mPFC (63,65). Albeit these heterogeneous results, the emerging trend points towards a decoupling of regular DMN configuration and activation patterns in experienced meditators, suggesting a shift towards a mode less prone to mind-wandering and self-referential thinking, and more rooted in present-moment awareness, in line with some of the main aims of meditation practice.

Meditation also re-configures the relations between the DMN and other large-scale brain networks. For the control network, ample evidence suggests increased FC between the PCC and dorsolateral PFC both at rest and during meditation (58,66,67). Additionally, increased general FC between DMN and FPN during meditation (61) has been reported, but also increased DMN-FPN anti-correlations as a trait following meditation practice (61,68), which were associated with better performance in a sustained attention task (68). For attention networks, various studies found increased FC with the DMN following meditation practice (69–71), while another (72,73) reported stronger DAN-DMN anti-correlations in experienced mediators compared to controls during rest and sustained attention. These findings may suggest that meditation entails more directed resting-state mental processes, while reducing mind-wandering during attention-based tasks. Additionally, increased FC with the DMN during meditation and at rest has been reported both for the salience network (74,75) and somatosensory networks (59,62,76). Taken together, these results suggest that as meditation practice proceeds, a reconfiguration of large-scale networks within the brain emerges, reflecting a greater capacity for sustained attention, meta-awareness and body-awareness, and a more fluid switching between internal and external attention, mediated by the salience network. We have highlighted the interactions among these networks across various attention and meditation states in Figure 1.

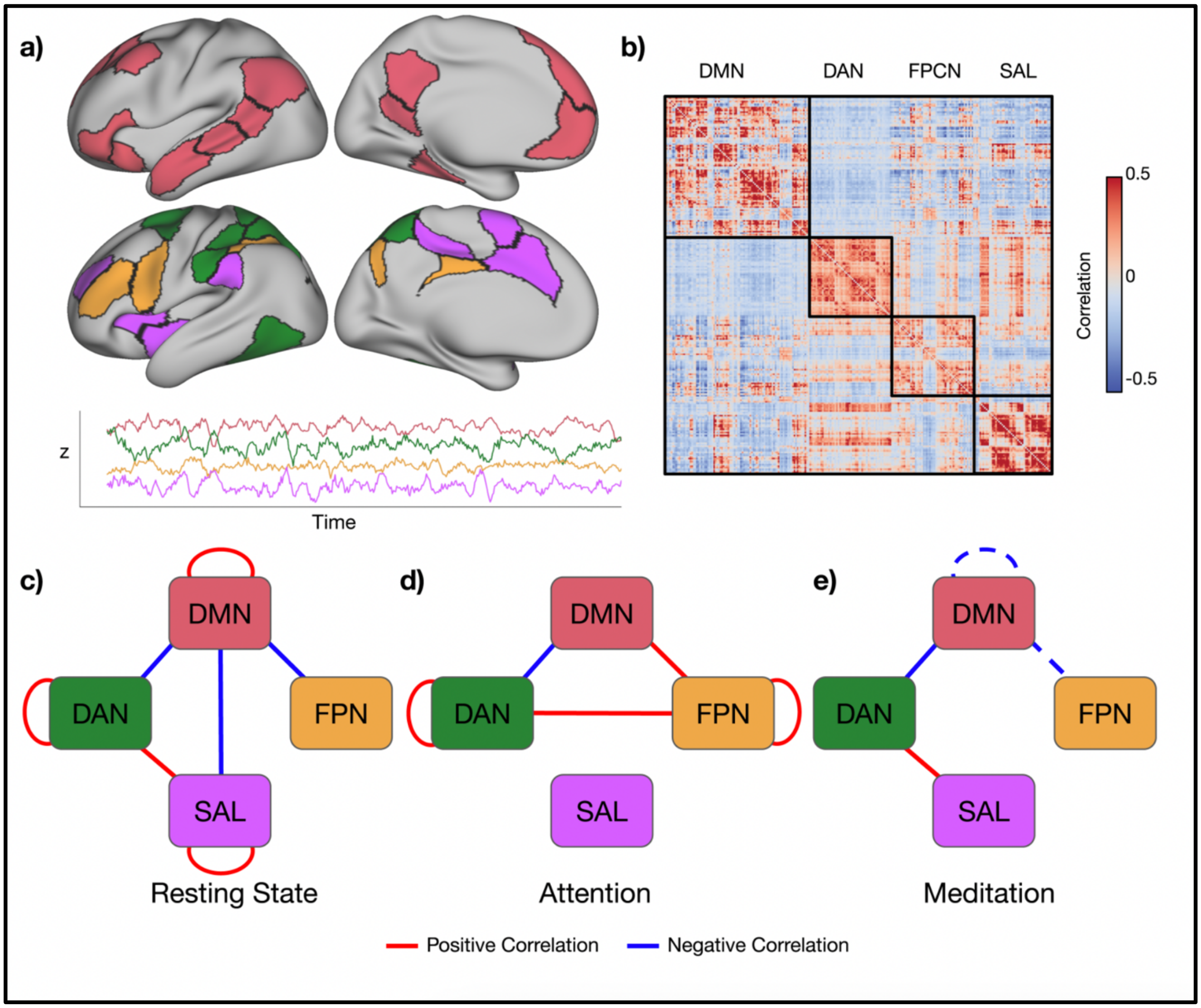

Figure 1: a) Top panel highlights the nodes of the DMN and other large-scale brain networks: DAN, FPN and SAL as defined using the 7-Network Yeo 2011 atlas. Bottom panel depicts the time series of the four networks in a resting-state condition for an example subject. The connectivity dynamically changes across the network's time. b) A depiction of the resting state functional connectivity matrix averaged across subjects for the four networks using the Schaefer 100 parcellation scheme. We see strong within-network connectivity but also within and across network heterogeneity highlighting the need of a common taxonomy and procedures for the estimation of these networks. Functional connectivity summary plots for the four networks for c) fixation based resting state (as computed on healthy subjects from the Human Connectome Project dataset as depicted in panel b) and for d, e) attention and meditation states (as observed from literature, see supplementary table 1 for reference to specific edges). Red line represents positive correlation and the blue line represents negative correlation (anti-correlation) within/between the networks. Dashed line highlights mixed results in the literature regarding the strength of the connectivity but more biased towards the highlighted color. Self-loops indicate within network connectivity.

DMN and clinical studies

1. Neurodevelopmental Disorders:

a. Autism Spectrum Disorder (ASD)

ASD is associated with deficits in social communication and interaction as well as mentalizing to infer mental states of others (82,83). Studies have demonstrated altered functional and structural organization of the DMN in individuals with ASD, with atypical developmental trajectories being prominent features (78). For example, most intrinsic FC studies in children with ASD report increased within-network connectivity between core DMN nodes, while studies in adolescents and adults report decreased connectivity, and studies in mixed age groups report both increases and decreases (79–84). These inconsistencies likely reflect developmental changes and heterogeneity in connectivity profiles across different nodes of the DMN. Nonetheless, aberrancies in key nodes of the DMN and impairments in flexibly attending to socially relevant stimuli have been generally observed, impacting social cognition in individuals with ASD and the strength of connectivity within DMN nodes has been associated with autism spectrum traits, suggesting a link between DMN connectivity and the level of autism spectrum traits (78,85,86).

b. Attention Deficit Hyperactivity Disorder (ADHD)

The earliest study (87) to link DMN integrity to ADHD found that in a group of diagnosed adults, decreased anti-correlation was observed between the posterior cingulate node of the DMN and the anterior cingulate cortex. Various fMRI studies have pointed to the enhancement of the activation of DMN areas in subjects with ADHD (88). Barring some diverse findings across task-based studies, the DMN is known to have an abnormal intrusion in the functioning of cognitive control networks, leading to lapses in attention that are often observed in subjects with ADHD (89).

2. Neurological and Neurodegenerative Disorders:

a. Alzheimer's disease (AD)

In the case of AD, while the integrity of the DMN decreases with aging even in healthy subjects, the FC of the DMN regions is found to be decreased in AD, especially in PCC and Precuneus areas (90). A systematic review showed that connectivity of DMN with SAL is increased in AD subjects (91) whereas the anti-correlations of DAN decreases with the DMN (92). Though some studies indicate FPN regions have increased connectivity with DMN (93), the literature has mixed findings (91).

b. Parkinson's Disease (PD)

Studies of PD have found that DMN function and connectivity is altered, particularly in patients with cognitive impairments. FC within the DMN was found to be negatively correlated with cognitive composite z-scores from cognitive tests across multiple domains (memory, attention, language, executive and visuo-spatial abilities) in patients, suggesting that increase in within-DMN connectivity and failure to suppress it during executive tasks are associated with cognitive decline in PD (94–96). Another study focused on DMN dysfunction during an executive task found PD patients exhibited less DMN deactivation during tasks that require externally-focused executive function (97)..

3. Mood and Anxiety Disorders:

a. Obsessive Compulsive Disorder (OCD) and Anxiety Disorders

Both anxiety and panic disorders are known to share common alterations in DMN connectivity (98). More specifically, the connectivity of DMN and SN has been found to be impacted in anxiety disorders (99). Interestingly, DMN-SN connectivity is known to be affected even in OCD, while OCD is also characterized by DMN hyperconnectivity with DAN and hypoconnectivity with visual areas (100).

b. Major Depressive Disorder (MDD)

The DMN has long been known for its role in emotional activity and regulation of self-referential processes in MDD (101). DMN is known to show increased intra-network as well as inter-network resting state functional connectivity in MDD studies. More specifically, while DMN is known to be anti-correlated with non-DMN networks like sensory and attentional networks, this anti-correlation is known to be replaced by an abnormally positive correlation in MDD groups (102,103). Similar findings have been observed with respect to decreased anti-correlation of the DMN with the CEN/FPN in MDD groups (104).

c. Post-Traumatic Stress Disorder (PTSD)

Alterations in DMN connectivity have also been observed in individuals with PTSD, particularly those with a history of early-life trauma (105). Studies have shown that individuals with PTSD exhibit hypoconnectivity within the DMN, especially in regions like the precuneus and right precuneus, compared to trauma-exposed controls (106–108). Furthermore, changes in resting-state FC of the DMN and other networks have been noted following cognitive processing therapy for PTSD, suggesting potential compensatory changes with treatment (109). These findings highlight the importance of understanding how alterations in DMN connectivity relate to the development and symptomatology of PTSD, especially in individuals with a history of early-life trauma.

d. Bipolar Disorder (BD)

Research has consistently shown DMN alterations in individuals with BD (110–112), a mental illness characterized by unusual shifts in mood, energy, activity levels, and concentration ranging from extreme highs (mania or “manic” episodes) to lows (depression or “depressive” episode (113)). In general the DMN alterations include reduced connectivity between the precuneus and DMN subsystems, increased connectivity in the midline core and dmPFC, stronger connections in the mPFC and IPL, and reduced DMN connectivity in the mPFC (110–112). Although DMN alterations are present in both the manic and hypomanic phases of bipolar disorder, DMN and sensory motor network (SMN) balance in terms of fractional stochastic dominance has been shown to be tilted towards the DMN in depression and towards the SMN in mania, suggesting a shift in resting-state structure (114). DMN in bipolar mania has been shown to be reduced in connectivity in the medial prefrontal cortex as well as altered activity in the DMN (115,116).

e. Schizophrenia (SZ)

Altered DMN connectivity in SZ is well known in the context of various attention tasks. Previous SZ studies have found evidence of changes in resting state FC (FC) between DMN and attention networks in the symptomatology of SZ groups (117–119). DMN connectivity in SZ is known to be increased between its midline hubs of mPFC and PCC (118,120,121), suggesting impaired self- and reality-monitoring. Moreover, increased FC between DMN and insula is well known (122), and may relate to diminished internal/external switching in SZ, given insula's role in mediation between DMN task-positive networks (2). In task paradigms, studies have found a stronger cue-induced DMN deactivation in a visuospatial attention task (123) and insufficient deactivation in a target detection task (124) in SZ groups. Impaired cognitive function in SZ is known to be linked with inefficient DMN suppression (125). Studies on audio-visual hallucinations further implicate the auditory cortices (i.e., superior and middle temporal gyri) based on their altered activation patterns during auditory processing (126) and altered FC with the DMN (127). It has been hypothesized that increased mPFC connectivity with the auditory cortices in the superior temporal gyrus (STG) may contribute to source misattribution of self-generated auditory content as external stimuli (128).

We have summarized the connectivity changes amongst the canonical networks for the various disorders in Figure 2 and have covered additional disorders in the supplemental section 1.

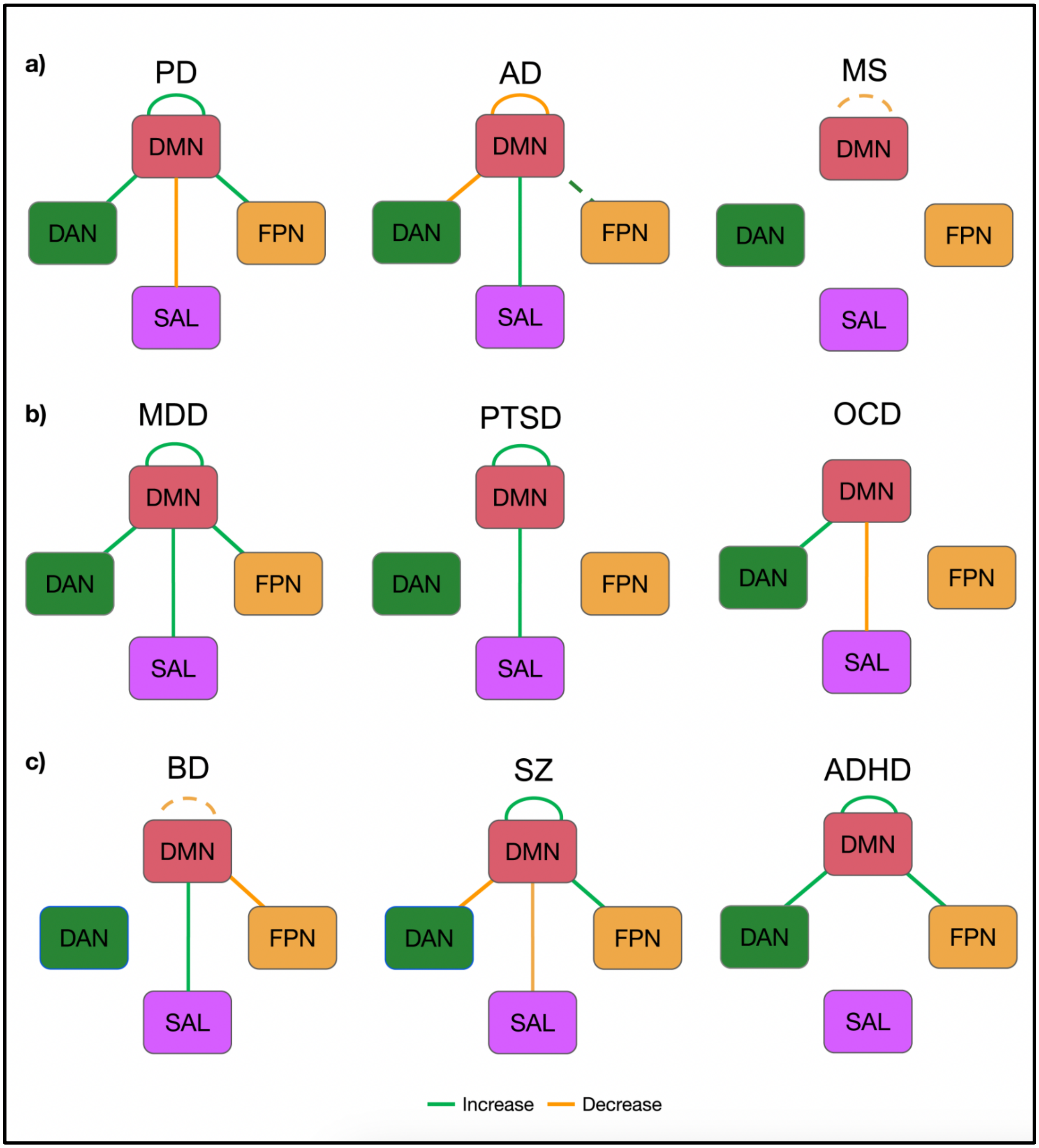

Figure 2: Highlighting the changes in the connectivity within and across the four networks: DMN, DAN, FPN and SAL across mental disorders with most consistent results as mentioned in the literature (see supplementary table 2 for reference to specific edges) a) Neurodegenerative disorders: Parkinson's Disease (PD), Alzheimer's Disease (AD), Multiple Sclerosis (MS); b) Mood and anxiety disorders: Mild Depressive Disorder (MDD), Post Traumatic Stress Disorder (PTSD), Obsessive Control Disorder (OCD); c) Developmental disorders: Attention Deficit Hyperactivity Disorder (ADHD), Bipolar Disorder (BD) and Schizophrenia (SZ). Green line/loop represents an increase in the amplitude of connectivity whereas orange line/loop represents decreased connectivity and the dashed line indicates mixed results in the literature.

fMRI Guidelines and Recommendations

Measuring between-network connectivity, such as DMN anti-correlations, crucially depends on the selection of network seeds and connectivity metrics—decision points that are hardly uniform across the field (129). Fortunately, methodological advances along with the hindsight of over two decades of fMRI research outline a set of recommended practices to guide such research. We review these topics here.

Network estimation

Network estimation is a data compression that transforms brain imaging data from the ‘microscale’ voxel to the ‘macroscale’ brain network. Many network estimation techniques are available today including dataset-derived parcellations (16,130), preset brain atlases (6,131–133), and functional mode atlases (134), each of which can be applied at the group- or subject-level. These different techniques have, unsurprisingly, a profound impact on connectivity results.

One of the greatest sources of variance introduced by network estimation is the obfuscation of meaningful subject-level signal structure that arises when averaging subject-level data in group-level analyses. Though group-level studies have long been the norm and provided many insights into the brain function and organization, there is growing recognition of the importance of subject-level precision fMRI given high structural and functional cross-subject spatial variance (1,8,135,136). Such cross-subject variance is highest in transmodal cortices including the DMN, FPN, and likely to a lesser extent, DAN (137,138). Strikingly, Bijsterbosch et al. (2018) found that up to 62% of the variance in simulated group-level FC network matrices is explained by cross-subject spatial variation in functional networks. This has profound implications for using group-level network connectivity as a biomarker.

Future research targeting DMN-related anti-correlations as biomarkers should face this cross-subject variance head-on by incorporating precision fMRI routines. Through preserving meaningful signal structure and allowing for more accurate modeling of variance (136), subject-level approaches would improve effect detection and interpretative clarity. Such an approach would be paramount, for instance, to understanding the differential contribution of DMN and FPN subsystems to anti-correlation biomarkers (see, for instance:(10)).

Barriers to precision fMRI include collecting enough data per participant (13,136,139) and the difficulty of group-level inference. Fortunately, advancements in fMRI acquisition with multi-echo sequences (10,140) and individualized areal estimation (16,141) are lowering the data collection barrier, while individualized-but-generalized parcellations (142) and forthcoming functional alignment procedures (142) may help allow broader inference. When precision approaches are not feasible, we recommend researchers compare results across network maps, such as with atlas-comparison tools (132).

Functional Connectivity estimation

FC is perhaps the most popular metric used to compute inter-regional communication in fMRI. It is also, somewhat circularly, inseparable from most network estimation methods (135,143). While a scoping review of FC estimation methods is beyond the scope of this review (though see (129)), certain practices have immediate relevance to measuring between-network anti-correlations.

One such practice is global signal regression (GSR), where the ‘global’ average time series is removed through linear regression. GSR has long been controversial in fMRI research due to its uncertain nature (144), non-uniformity (145), and profound effect on connectivity estimates including anti-correlations (146). An emerging understanding of GSR is that it resembles a composite of both neural and non-neural sources (144,147) whose removal increases anti-correlations between brain systems by virtue of mean centering and noise removal (146). Effects that are unreproducible without GSR may not be analysis artifacts in as much as they reflect neural features whose detection benefits from removal of shared trends (146). In general, and especially for research focused on brain system anti-correlations, we recommend reporting results both with and without GSR.

Alternative metrics for inter-regional communication should also be explored. For instance, the bivariate correlation underlying most FC approaches measures only a subset of the information architecture of the brain and even BOLD signal (143,148), with particular relevance for transmodal networks (149). While FC reflects redundant information equally carried by multiple sources, partial entropy-related measures can compute synergistic information that is necessarily supported by multiple sources (143,148).

Conclusions and Future Directions

In the current review, we looked at the resting state FC between DMN and other brain regions in healthy subjects, during attentional processes, meditation and highlighted how it changes with various clinical conditions. We concluded with general guidelines on how to robustly measure this relationship. Overall, the DMN plays an integrative role internally-oriented and an antagonistic role during externally-oriented cognitive control and attention. It allow for elaborate scene construction, episodic projection, internal mentation and thinking about others. Disorders like depression, schizophrenia, and ADHD feature marked alterations to DMN activity and connectivity with control and attention networks. Such changes appear linked to reduced control over intrinsic activity as well as reduced ability to switch between extrinsic and intrinsic modes of processing. The ease of collecting FC data gives us a potential utility of DMN anti-correlations as a biomarker of mental health and disorders and how therapeutic interventions including meditation paradigms allow the maintenance of DMN health. More work is needed on making the DMN anti-correlations measure robust across individual healthy subjects and increasing its clinical viability which would require a clear definition of networks where precision imaging approaches will help. The development of standardized collection and preprocessing frameworks will also help.

As we move forward, several avenues warrant further exploration to deepen our understanding of the DMN and its implications as a biomarker for cognitive health: a) Precision fMRI Methods: Embracing subject-level precision fMRI approaches will enable researchers to better capture individual variability in DMN connectivity, enhancing the reliability and interpretability of findings. b) Advanced Connectivity Metrics: Investigating alternative metrics beyond traditional BOLD FC, such as partial entropy-related measures, may unveil novel insights into the complex dynamics of DMN interactions. c) Integration of Multimodal Imaging: Combining fMRI with other modalities like EEG-fMRI or MEG can provide a more comprehensive understanding of the neural bases underlying DMN-related anti-correlations, offering valuable insights into brain-behavior relationships (150). d) Clinical Translation and Intervention: Translating research findings into clinical practice, including the development of targeted interventions leveraging DMN modulation, holds promise for improving treatment outcomes in psychiatric disorders. e) Longitudinal Studies and Biomarker Development: Longitudinal studies tracking DMN connectivity changes over time, coupled with biomarker development efforts, are crucial for elucidating disease trajectories and identifying early markers of cognitive decline or psychiatric vulnerability f) Mega-Analysis studies like the ENIGMA consortiums to aid in large-scale development and validation of DMN biomarkers.

By embracing these future directions, we could unlock new frontiers in DMN research, advancing our knowledge of brain function and facilitating the development of innovative strategies for mental health diagnosis and intervention.

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Supplemental Section 1

Multiple Sclerosis (MS)

Recent evidence from studies on multiple sclerosis (MS) suggests that higher order networks, such as the DMN, are more likely to experience alterations to structural damage than lower order networks (e.g., visual) (1). As such DMN nodes including the ACC and PCC have been found to be altered suggesting a link between depression and cognitive impairment in MS (2,3). These alterations are known to take place in terms of the DMN's functional connectivity (3), structural integrity and cerebellar connectivity (4), centrality in the functional network hierarchy (5) as well as dynamic functional connectivity (dFC) in task paradigms (6). MS thus, can be considered a network disorder, with damage leading to a "network collapse" and clinical progression (7).

Traumatic Brain Injury (TBI)

Abnormal DMN connectivity has been observed in patients with mTBI, providing insights into how neuronal communication and cognitive processes may be affected following such injuries (8). This DMN disruption may persist long after the initial injury and impact everyday functioning, highlighting the importance of understanding how changes in the DMN relate to cognitive outcomes in individuals with TBI (9). A hyperconnectivity within the DMN is being discussed as a potential biomarker for PCS (10), and recent studies suggest a reduced DMN-CEN anticorrelation in patients experiencing PCS (10,11).

Addiction Disorders

Aberrant patterns of brain functional connectivity have been observed within the DMN as well as between DMN and cortical regions involved with executive function, memory and emotion across different classes of substance use disorder (SUD) and are associated with craving and relapse (12,13). For instance, it has been observed that in general anterior DMN nodes tend to show decreased FC while posterior nodes tend to have increased FC. These alterations are believed to contribute, on the one hand with impaired self-awareness, negative emotions, and rumination, and on the other with a lack of cognitive control and drug-taking behaviors regardless of negative consequences. These alterations have been observed in various types of addiction, including SUD like alcohol (14–17), nicotine (18–21), cannabis (22–24) and cocaine (25–28) as well as non-SUDs like gambling (29) or internet (30) addictions. In general, these alterations in DMN connectivity have been suggested to contribute to impaired self-awareness and negative emotions as well as affecting cognitive control and memory encoding. These alterations in DMN connectivity are linked to changes in dopaminergic, glutamatergic, and GABAergic signaling associated with addiction (12,13,15,31).

Supplementary Table 1: Highlighting the key references that informed the edges in Figure 1d and 1e for attention and meditation states.

State	Edges (References)
Attention	DMN-DAN (32), DMN-FPN (33), DAN-DAN (34), DAN-FPN (34), FPN-FPN (34)
Meditation	DMN-DMN (35–37), DMN-DAN (32,38–41), DMN-FPN (42,43), DAN-SAL(44,45)

Supplementary Table 2: Highlighting the key references that informed the edges in Figure 2 for various disorders including Parkinson's Disease (PD), Alzheimer's Disease (AD), Multiple Sclerosis (MS); Mild Depressive Disorder (MDD), Post Traumatic Stress Disorder (PTSD), Obsessive Control Disorder (OCD); Attention Deficit Hyperactivity Disorder (ADHD), Bipolar Disorder (BD) and Schizophrenia (SZ)

Disorder	Edges (References)
PD	DMN-DMN (46–48), DMN-DAN (49,50), DMN-FPN (46–48,51), DMN-SAL (46–48,51)
AD	DMN-DMN (52), DMN-DAN (54), DMN-SAL (56), DMN-FPN (58)
MS	DMN-DMN (2,3)
MDD	DMN-DMN (53), DMN-DAN (55,57), DMN-SAL (55,57), DMN-FPN (59,60)
PTSD	DMN-DMN (61–63), DMN-SAL (61–63)
OCD	DMN-DAN (64), DMN-SAL (65,66)
BD	DMN-DMN (67), DMN-SAL (68), DMN-FPN (59,68)
SZ	DMN-DMN (69–71), DMN-DAN (70,72,73), DMN-FPN (74), DMN-SAL (75)
ADHD	DMN-DMN (76,77), DMN-DAN (77), DMN-FPN (78)

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