

Aberrant Coupling of the Default Mode Network in Psychiatric Disorders: From Structural–Functional Integration to Network Dysfunction

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Abstract—The Default Mode Network (DMN) is a large-scale brain system involved in self-referential processing, memory, mentalizing, and internally directed cognition. Increasing evidence suggests that abnormalities in the relationship between brain structure and function may contribute to psychiatric disorders, but the pattern of structure–function coupling within the DMN is not consistent across conditions. This review examines recent evidence on DMN-related Structural–Functional Connectivity (SC–FC) coupling in Major Depressive Disorder (MDD), schizophrenia, autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD). Across these disorders, altered SC–FC coupling is observed at regional and network levels, but both increased and decreased coupling have been reported. MDD is characterized by increased coupling in several DMN-related regions, whereas schizophrenia shows a more heterogeneous pattern involving both increased and decreased coupling. ASD also shows multidirectional alterations between the DMN and other large-scale systems, while ADHD demonstrates regional, subtype-, and development-dependent differences in coupling. These findings suggest that psychiatric disorders are unlikely to be defined by a uniform abnormal direction of SC–FC coupling. Changes in the ratio of structural limitations to functional flexibility may instead be reflected in changing coupling. Since structure–function coupling changes throughout childhood and adolescence, development is crucial in understanding these anomalies. In order to differentiate disorder-related changes from normal developmental variation and to determine whether DMN SC–FC coupling can be a useful indicator of common and disorder-specific mechanisms across psychiatric conditions, future longitudinal and transdiagnostic research is therefore required.

Keywords—Default Mode Network (DMN), coupling, neurodevelopment, transdiagnostic research

I. INTRODUCTION

The Default Mode Network (DMN), a large-scale brain network, performs several inwardly focused cognitive functions and exhibits comparatively high intrinsic activity when at rest [1]. The precuneus, lateral parietal, medial temporal lobes, Posterior Cingulate Cortex (PCC), and

medial Prefrontal Cortex (mPFC) are among its primary regions [2]. The DMN facilitates self-referential processing, autobiographical and episodic memory, mentalizing, and the production of internally directed thoughts through interactions across these dispersed regions [2, 3]. Crucially, the DMN dynamically interacts with other large-scale networks involved in salience processing and cognitive control rather than operating alone. Abnormalities in DMN organization and network-level interactions may represent a common hallmark of psychopathology, as disruption of these connections has been linked to a variety of psychiatric illnesses, including depression, schizophrenia, anxiety, and autism [4]. As a result, studying the DMN offers a crucial framework for comprehending how changes in the organization of the brain network may be linked to a variety of mental illnesses.

II. EVIDENCE OF PSYCHIATRIC DISORDER

A. Major Depressive Disorder (MDD)

Major Depressive Disorder (MDD) is a recurrent psychiatric disorder. It is characterized by a persistent depressed mood, a loss of interest and anhedonia [5]. Because of its recurrent nature and its substantial effects on daily functioning, MDD is considered as an important contributor to the global burden of disease and as one of the main causes of disability around the world [5, 6].

People with MDD are linked to brain morphology abnormalities [7], including reduced cortical thickness [8], less gray matter [9], a smaller surface area [10], and abnormalities in white matter fibers such as demyelination [11], abnormalities in Fractional Anisotropy (FA) [12], and reduced structural connectivity [13].

Previous studies indicated that MDD patients showed aberrant within-and-between large-scale brain network functional connectivity of DMN, Salience Network (SN), and Frontoparietal Network (FPN) [14, 15], which was correlated with the clinical symptom severity in MDD [16]. Recently, increased regional Structural and Functional Connectivity (SC–FC) coupling was found within the

DMN of MDD patients compared to Healthy Controls (HCs) [17], which was interpreted as reflecting more functional dynamics constrained by the underlying structural architecture [18]. Moreover, in adolescent patients with depression, increased SC–FC coupling was observed in several hub regions of DMN and visual networks compared to HCs, including precuneus, inferior parietal gyrus, insula, and medioventral occipital gyrus, reflecting excessive anatomical constraints on functional communication, impaired network reconfiguration, and maladaptive engagement of cognitive processes [18].

Beyond intrinsic DMN abnormalities, MDD also shows abnormalities in the interaction between the DMN and other large-scale networks. Abnormal functional coupling between the DMN and other networks has also been reported, including the hyperconnectivity between regions of the DMN and FPN [14]. This presumably reflects the depressive tendency to focus more on internal thoughts than external interactions, suggesting impaired regulation of negative self-referential processing and reduced cognitive flexibility [19, 20]. According to the triple-network model, the Salience Network (SN) functions as a switching system detecting salient internal and external cues and thereby regulating the interplay between the DMN and FPN [4]. Dysfunctional interactions among the DMN, SN, and FPN may disrupt the coordination between internally directed cognition and executive control that has been linked to the persistent rumination, impaired emotional regulation, and cognitive dysfunction, characteristic of MDD [14, 20].

B. Schizophrenia

Schizophrenia is a psychiatric disorder that is highly varied and in which the symptoms usually include those that are classified as positive, negative, and cognitive [21]. Hallucinations, delusions, and disturbances of thinking and behavior are examples of good symptoms; decreased motivation, less spontaneous speech, restricted emotional expression, and social disengagement are examples of negative symptoms. Attention, working memory, executive functioning, and information processing are just a few of the cognitive issues that are frequently observed. Individual differences in the combination and intensity of these symptoms highlight the disorder's clinical variability [22]. The fact that schizophrenia exhibits a wide variety of symptoms have been connected to disturbances in a number of higher-order cognitive processes, including self-observation, social cognition, perception, and the incorporation of data that is both locally and externally produced [23–26]. Large-scale brain systems and various association cortexes combine to provide these cognitive tasks [3, 27, 28]. As a result, schizophrenia is now more commonly explained in terms of impaired communication between distributed brain systems rather than as a result of dysfunction in a single anatomical area.

The DMN is a group of associative cortical regions generally associated with advanced cognitive functioning in health and schizophrenia [2]. Many studies have linked DMN malfunction in schizophrenia with many positive and negative symptoms, such as delusional experiences,

hallucinations, and disorganized thought and behavior [29–32].

Abnormal connectivity between large-scale networks and the DMN can provide insight into the longstanding “disconnection hypothesis” that explains schizophrenia pathophysiology as coupling impairments due to context-dependent synaptic modulation [27, 33]. Several studies have reported hypoconnectivity between regions of the DMN, such as between the Posteromedial Cortex (PMC) and the Temporoparietal Junctions (TPJ) [29, 30, 34]. Other investigators instead reported hyperconnectivity within the DMN, such as between the medial prefrontal cortex and the PMC [32, 35]. Frequently inconsistent findings have also been published on pathological connectivity between the DMN and other commonly observed multimodal networks. For example, coupling of the DMN with the Dorsal Attention Network (DAN) as well as coupling between the DMN and the Salience Network (SN) were reported as pathologically decreased by some [36, 37] and as pathologically increased by others [38]. Recent study has also revealed that functional covariation analyses highlighted dysfunctional DMN–DAN coupling, structural covariation results highlighted aberrant DMN–SN coupling, and across structural covariation analyses, the PREC emerged as one of the most impaired DMN nodes [39]. Focusing inside the DMN, studies have shown that compared with controls, patients showed an increased SC–FC coupling in the DMN and the central modules. Moreover, significant SC–FC decoupling was demonstrated in the occipital and subcortical modules, which was associated with longer duration of illness and more severe clinical manifestations of schizophrenia [40]. These inconsistent results imply that schizophrenia may be characterized by disturbed network organization and reduced flexibility rather than a consistent rise or fall in DMN connectivity.

C. Autism Spectrum Disorder (ASD)

Autism Spectrum Disorder (ASD) is a diverse neurodevelopmental illness marked by limited or repetitive patterns of behavior and interests, as well as ongoing challenges with social communication and interaction [41]. The disorder's varied developmental and molecular causes are reflected in the significant variation in clinical presentation that has been documented [42, 43]. As a result, neuroimaging research has revealed structural and functional changes in brain organization, indicating that ASD is linked to abnormal coordination among dispersed neural systems rather than dysfunction in a single brain region [44, 45].

According to functional neuroimaging research, people with ASD exhibit aberrant DMN architecture, which includes changed connections including the inferior parietal areas, medial prefrontal regions, and posterior cingulate cortex [46, 47]. Such alterations have been linked to difficulties in social and self-related processing, although the direction and spatial distribution of DMN abnormalities may vary across individuals and developmental stages. Studies of children with ASD, for example, have identified heterogeneous alterations within the posteromedial components of the DMN, with some

connectivity differences related to the severity of social deficits [48]. These findings suggest that atypical DMN organization may contribute to the social-cognitive difficulties characteristic of ASD [48, 49].

More recently, attention has shifted from functional connectivity alone to the relationship between structural and functional brain organization. The degree to which functional connectivity between brain regions aligns with their underlying structural architecture is measured by SC–FC coupling [50]. This link may also be disrupted across large-scale brain systems, according to evidence from ASD. In their analysis of higher-order structural-functional coupling, notable distinctions between people with ASD and those who are typically developing in a number of network pairs are found [51]. Specifically, the DMN's connections with the motor, visual, auditory, and limbic/salience-related systems showed changed coupling; depending on the structural connectivity measure analyzed, both increased and decreased coupling were found. These results suggest a more intricate reconfiguration of the link between structural limitations and functional communication in ASD rather than a consistent increase or decrease in SC–FC coupling.

When considered collectively, the available data indicates that anomalies in the coordination of large-scale brain networks at both the functional and structural-functional levels are linked to ASD. The idea that atypical network integration may lead to impaired social cognition and more general behavioral traits of ASD is supported by the DMN's recurrent engagement as well as changed coupling between the DMN and other sensory, motor, and higher-order systems. Crucially, rather than being a straightforward pattern of global hyperconnectivity or hypoconnectivity, ASD may be best described as a disorder of altered network organization and flexibility due to the coexistence of enhanced and decreased SC–FC coupling across many network interactions.

D. Attention-Deficit/Hyperactivity Disorder (ADHD)

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental condition characterized by persistent problems with impulsivity, hyperactivity, and attention management [52]. Despite the fact that their clinical presentation varies, these symptoms can have a substantial impact on daily behavior, academic performance, and cognitive functioning [53].

Despite the lack of significant group differences in functional connectivity alone, children with ADHD had changed structural network architecture and decreased network efficiency within the DMN when compared to typically developing controls [54]. Notably, differences were more apparent when structural and functional organization were examined together [54]. Children with the mixed ADHD presentation showed stronger DMN coupling than those with the primarily inattentive presentation and higher SC–FC coupling throughout numerous subnetworks, including the DMN, when compared to typically developing children. These results underscore the neurobiological variety among ADHD

presentations and imply that SC–FC coupling may capture abnormalities that are difficult to identify by structural or functional connectivity measures taken independently [54, 55].

Additionally, developmental studies suggest that rather than just being generally enhanced or diminished, SC–FC coupling in ADHD may follow an abnormal trajectory (56). In typically developing children, structure–function coupling often increased with age, especially across regions implicated in higher-order cognitive and sensory processing [56]. However, coupling was decreased in a number of cortical regions in ADHD, while an abnormally rapid age-related increase was observed in some locations. The discrepancy between these regional trajectories raises the possibility that impaired coordination between brain growth and functional specialization may be the cause of abnormal SC–FC coupling in ADHD. Therefore, there may be a discrepancy between the ongoing refinement of functional network architecture and structural growth in the neuronal phenotype of ADHD.

This perspective is further supported by recent data from people with co-occurring neurodevelopmental disorders. When comparing those with ASD and comorbid ADHD to those with ASD alone, researchers found different SC–FC coupling patterns, including greater coupling in cerebellar areas linked to socio-emotional and DMN-related processing [57]. These results suggest the idea that ADHD-related changes go beyond classical cortical networks and may involve cerebella-cortical connections that interact with higher-order cognitive systems, however they should be taken cautiously due to the cross-diagnostic approach. When combined, data from comorbidity investigations, developmental studies, and subtype comparisons show that SC–FC coupling anomalies in ADHD are marked by significant regional and developmental variation. These changes seem to be dependent on the developmental stage, brain region, and symptom presentation rather than a consistent increase or decrease in coupling. This pattern is typically comparable with findings in other neuropsychiatric disorders and supports the potential utility of SC–FC coupling as a framework for investigating how abnormal structural–functional integration contributes to ADHD.

III. DISCUSSION

One important finding from the literature is that not every part of the brain should be viewed in the same way when it comes to changes in structure-function coupling. Throughout the cortex, structure-function coupling is arranged hierarchically, with comparatively stronger coupling in unimodal sensory regions and weaker coupling in trans-modal association areas. The latter pattern has been referred to as structural “untethering”, which may facilitate more flexible types of cognition by enabling functional activity in higher-order regions to become less restricted by their underlying anatomical connections [58]. Importantly, this relationship is not static across development. During youth, changes in structure–function coupling are particularly prominent in trans-modal cortex, suggesting that the relationship between brain structure

and function continues to be reorganized as higher-order cognitive systems mature [59]. From this perspective, an increase in coupling does not necessarily indicate a pathological process, just as reduced coupling does not necessarily represent functional impairment. The meaning of a coupling abnormality may depend on where it occurs, how the region normally develops, and the functional role of the network involved.

Across the four disorders reviewed here, several common patterns can nevertheless be identified. First, abnormalities in DMN-related structure–function coupling have been reported across MDD, schizophrenia, ASD, and ADHD, although the specific regions and directions of change differ between disorders. In MDD, increased regional SC–FC coupling has been reported within the DMN, whereas schizophrenia shows a more heterogeneous pattern involving both increased and decreased coupling across different modules [17, 40]. While studies of ADHD indicate that coupling anomalies differ according to developmental stage and clinical subtype, recent data in ASD has also revealed aberrant coupling involving the DMN and other network modules [51, 54, 56]. When combined, these results imply that a single direction of SC–FC abnormalities is unlikely to be indicative of psychiatric illnesses. Rather, a more comprehensive reconfiguration of how structural limitations influence functional communication may be reflected in changed coupling.

An important difference between the disorders concerns the extent to which developmental factors may contribute to these coupling patterns. The evidence reviewed here does not come from a single developmental window: MDD and schizophrenia studies include both adolescent and adult populations, whereas much of the ASD and ADHD evidence is derived from younger samples. This distinction is particularly important because SC–FC coupling itself changes during childhood and adolescence. Therefore, an apparently increased or decreased coupling pattern may represent different processes depending on the developmental stage at which it is observed. For example, the increased rate of coupling development reported in some regions in children with ADHD should not automatically be interpreted as accelerated maturation. Without comparison with age-specific normative developmental trajectories, the same pattern could reflect a delayed, compensatory, or otherwise atypical trajectory of network maturation [56]. This issue is especially relevant when attempting to compare neurodevelopmental and psychiatric disorders across studies, because diagnostic differences may partly overlap with differences in age and developmental stage.

Additionally, the existing evidence has a number of methodological flaws. First, there may be discrepancies in results because different research defines brain regions, employ different imaging modalities, and compute SC–FC coupling in different ways. Second, the majority of research that is currently accessible is cross-sectional, which makes it challenging to ascertain if abnormal coupling occurs before symptoms appear, develops as a result of disease, or shifts as symptoms worsen. Third,

observed coupling patterns may be further influenced by the inconsistent control of medication exposure, illness duration, and psychiatric comorbidities among investigations. Because of these constraints, it is challenging to ascertain if disrupted DMN coupling is a common neuroimaging result of many illnesses or a shared transdiagnostic process.

Therefore, future research should do more than just determine whether coupling is higher or lower. To separate aberrations associated to disorders from normal developmental changes, longitudinal designs using age-matched healthy controls are required. Multimodal imaging may also help clarify how changes in white-matter organization and functional communication develop together over time. In addition, transdiagnostic studies using comparable imaging and coupling methods could determine which abnormalities are shared across disorders and which are specific to particular diagnoses. Recent work comparing dynamic structure–function coupling across major psychiatric disorders supports this direction, showing that psychiatric conditions can exhibit both shared and disorder-specific alterations at different levels of brain organization [60]. Overall, the existing evidence suggests that DMN SC–FC coupling is better understood as a dynamic property of brain organization rather than a fixed pathological marker. Its clinical significance may depend on the interaction between brain region, developmental stage, and disorder-specific network dysfunction.

IV. CONCLUSION

Overall, the literature reviewed here suggests that aberrant DMN SC–FC coupling is a shared but highly heterogeneous feature across MDD, schizophrenia, ASD, and ADHD. The available evidence does not support a simple model in which increased coupling represents dysfunction and decreased coupling represents impairment. Instead, the functional meaning of altered coupling appears to depend on the cortical hierarchy, the region or network involved, and the developmental stage at which the alteration occurs. The relatively weak structure–function relationship observed in transmodal cortex may provide the flexibility required for higher-order cognition, while developmental remodeling of this relationship continues throughout childhood and adolescence [58, 59]. Abnormal coupling may therefore reflect an altered balance between structural constraints and functional flexibility rather than a single pathological direction.

Across disorders, MDD shows relatively prominent increases in DMN-related coupling, schizophrenia demonstrates a mixed and region-dependent pattern, ASD shows altered coupling between the DMN and several sensory and higher-order systems, and ADHD is particularly characterized by developmental and subtype-related variation [17, 40, 51, 54, 56]. These variations imply that both disorder-specific patterns of network breakdown and common changes in brain architecture may be captured by DMN SC–FC coupling. However, the majority of current research is still based on

cross-sectional studies, and direct comparisons between illnesses are limited by variations in age, brain parcellation, imaging techniques, and coupling estimates.

Therefore, longitudinal, age-matched, multimodal, and transdiagnostic techniques should be given more attention in future study. When assessing coupling abnormalities in teenagers, it is especially important to take developmental trajectories into account rather than accepting a greater or lower coupling value as proof of rapid or impaired maturation on its own. The necessity to differentiate shared from disorder-specific changes is further supported by recent research on dynamic structure–function interaction across psychiatric diseases [60]. When considered collectively, DMN SC–FC coupling might be better understood as a dynamic indicator of how structural design either permits or restricts functional organization. A more helpful framework for examining the brain mechanisms underlying psychiatric diseases may be provided by comprehending this link in the context of development and clinical heterogeneity.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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