

Developmental Resting State Functional Connectivity for Clinicians

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Abstract Resting state functional magnetic imaging (fMRI) is a novel means to examine functional brain networks. It allows investigators to identify functional networks defined by distinct, spontaneous signal fluctuations. Resting state functional connectivity (RSFC) studies examining child and adolescent psychiatric disorders are being published with increasing frequency, despite concerns about the impact of motion on findings. Here we review important RSFC findings on typical brain development and recent publications on child and adolescent psychiatric disorders. We close with a summary of the major findings and current strengths and limitations of RSFC studies.

Keywords Functional connectivity · Resting state · Brain development · Functional MRI

Introduction

For decades, acquiring functional magnetic resonance imaging (fMRI) scans while research participants complete tasks has been the “gold standard” technique for understanding human brain function. However, over the last 5 years, publications and scientific presentations on “resting state fMRI,”

“resting state functional connectivity,” or “intrinsic functional connectivity” have become quite common. Here we briefly summarize this new brain imaging technique and its relevance to understanding the developing brain. Specifically, we review studies of typical development that have examined how resting state functional connectivity (RSFC) changes across development and in some of the most common psychiatric disorders seen in youth: autism spectrum disorders (ASD), mood and anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), and psychotic disorders. We conclude with a summary and discussion of concerns that have been raised about this novel neuroimaging technique.

What Is Resting State Functional Connectivity?

RSFC is a term commonly used in the scientific literature to describe a form of fMRI used in research studies where, in contrast to traditional fMRI scan paradigms, there is no specific task for the participants to complete; rather, the scan is acquired while the subject is “at rest.” Typically, participants are asked to lie still and to not think about anything in particular. Many studies provide instructions for participants to stay awake with their eyes closed, while others instruct participants to keep their eyes fixed on a neutral stimulus, such as a cross, throughout the scan. The primary principle underlying RSFC is that the pattern of low-frequency fluctuations in the blood oxygen level-dependent (BOLD) signal is highly correlated between brain regions that form functional circuits, even in the absence of an experimental task (Fig. 1) [1••]. Resting state networks discussed in this paper are visually depicted in Fig. 2 [2]. RSFC allows for more facile comparisons across research sites and enables the study of brain function in populations that are typically excluded from task-based MRI studies (i.e., infants and developmentally

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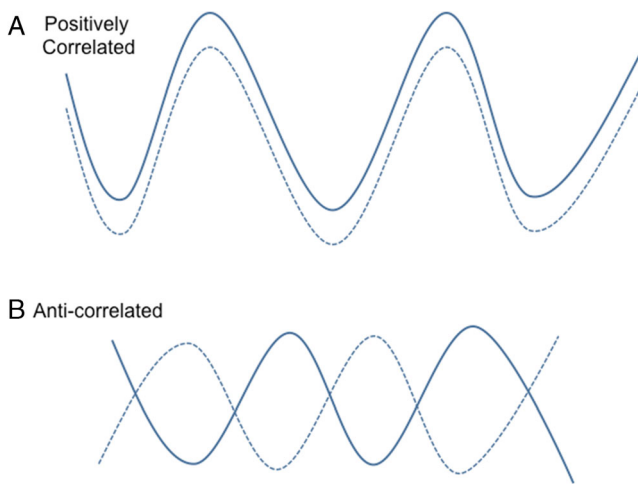


Fig. 1 The waveforms in **A** and **B** represent the low-frequency blood oxygen level-dependent (BOLD) signal fluctuations (x-axis) originating from two distinct locations in the resting brain, over time (y-axis). **A**. “Positively” correlated waveforms that are often referred to as “positive resting state functional connectivity.” **B**. Anti-correlated or “negative resting state functional connectivity” between two regions

disabled subjects). Currently, the utility of RSFC is limited to non-clinical research settings.

Typical Development

Changes During the First 2 Years

RSFC has been studied in infants as young as 2 weeks of age. The earliest infant study identified five functionally and spatially independent brain networks in 24- to 27-week-old-infants ($n=12$) [3]. Each of these networks has been described in adults, although the authors noted the absence of one of the best-characterized RSFC networks, the default mode network (DMN). The DMN comprises the medial prefrontal, posterior cingulate, temporal, and parietal cortices, which have been shown to be active, as a network, during rest or during low-cognitive-demand tasks [4]. Theories about the function of the DMN include “the retrieval and manipulation of episodic memories and semantic knowledge” [4], social or self-

referential processing [5, 6], or stimulus-independent thought [7, 8].

Another study, which compared 2- to 4-week-olds ($n=28$), 1-year-olds ($n=26$), and 2-year-olds ($n=21$), reported that RSFC strength increased with age, with a more rapid developmental trajectory being noted for sensorimotor as opposed to visual networks [9]. More recently, Gao and colleagues [10] examined RSFC in neonates ($n=51$), 1-year-olds ($n=50$), and 2-year-olds ($n=46$), and found that two well-known networks (the DMN and dorsal attention, which is thought to consciously orient attention toward stimuli [11]) evolved from isolated regions in neonates to cohesive networks by the age of 1 year, with further expansion/strengthening of the networks by the age of 2 years [10]. Whereas adult research has shown that these networks are anti-correlated (i.e., the regions oscillate out of sync with each other [12]), this study found that the anti-correlation was absent at birth but became apparent by the age of 1 year and was further enhanced by the age of 2 years [10]. Thus, primitive RSFC networks appear to be present early in infancy but mature rapidly over the first 2 years of life.

Changes from Childhood to Adulthood: Integration, Segregation, Homotopy and Anti-correlations

Several different techniques have been used to study changes in development in RSFC networks from childhood to adulthood. However, findings characterizing RSFC across development must be considered with caution, in light of recent work suggesting that head motion likely impacts and even negates some of these findings, as discussed in more detail below (see “Conclusions”). In a series of studies, Fair and colleagues examined RSFC differences between children, adolescents, and adults. They first examined attention control networks and found that each developmental phase was associated with an increase in long-distance connections (interpreted as improved “integration”) and a decrease in short-range connections [13••]. They also found that four networks spanning the brain (DMN, frontoparietal, cingulo-opercular, and cerebellar) showed increased integration and segregation across development [14, 15]. Utilizing a large sample ($n=100$) of 12- to 30-year-olds, Stevens and

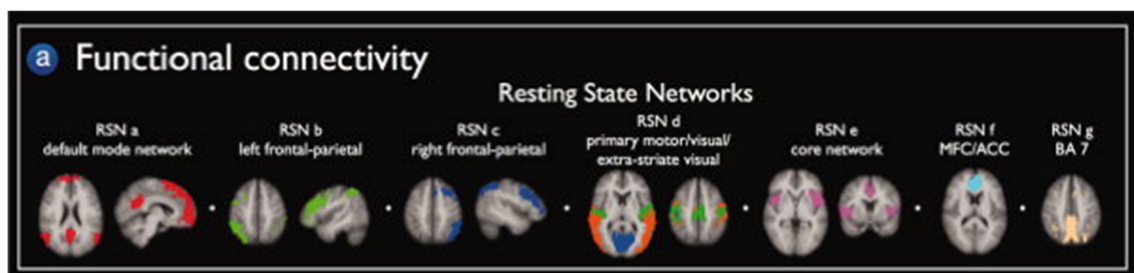


Fig. 2 Group clustering of resting state fMRI data revealed nine resting state networks (RSNs) of functionally linked cortical regions (reproduced with permission from van den Heuvel et al. [2]). *ACC* anterior cingulate cortex, *BA* Brodmann area, *MFC* medial prefrontal cortex

colleagues also found that increasing age was associated with within-network connectivity growth and more efficient between-network connectivity [16].

Kelly and colleagues examined RSFC development of anterior cingulate cortex (ACC) networks from childhood through adulthood [17]. As in the studies above, they noted a decrease in short-range (local) connectivity with age, and an increase in long-range connectivity. Further, they noted that the greatest degree of developmental change was observed in emotionally relevant regions (originating in the subgenual ACC [sgACC]) and a network of regions involved in social processing (originating in the perigenual ACC [pgACC]). RSFC has also been used to predict individual brain maturity [18•, 19], with the greatest predictive power being within the cingulo-opercular network, a network thought to be involved with cognitive control [20]. Brain maturity was associated with overall weakening of between-network connections and strengthening of within-network connections [18•].

Zuo and colleagues examined homotopy, or the degree to which regions in each hemisphere are connected, of RSFC networks across development [21]. In addition to age-related changes, they found sex differences in homotopy, where females had greater homotopy in the posterior cingulate cortex, medial prefrontal cortex, and middle and superior frontal cortex, but males had greater homotopy in the cerebellum, parahippocampus, and fusiform cortex. Further, there was a sex by age interaction for the dorsolateral prefrontal cortex and amygdala, where females and males showed opposite developmental trajectories.

Narrowing in on specific networks, a recent study examined “task-positive” RSFC networks (the intraparietal sulcus, frontal eye fields, and middle temporal region; regions routinely exhibiting task-related *activations* [22]; also known as the “ventral attention network”) and “task-negative” RSFC networks (similar regions to the DMN; regions routinely exhibiting task-related *deactivations* [22]) in children (n=63) and adults (n=28) [23]. They found that adults showed greater connectivity between the task-positive network and the dorsolateral prefrontal cortex, and stronger anti-correlations between the task-negative network and the anterior insula, parietal, and posterior cingulate cortices [23]. Chai and colleagues also examined the development of anti-correlated networks in 8- to 24-year-olds [24] and found that as age increased, anti-correlations also increased between networks (i.e., between the medial and dorsolateral prefrontal cortex, and between the lateral parietal cortex and supramarginal gyrus and precuneus). The authors noted that the correlation between regions in these networks was positive in childhood but negative in adulthood, with adolescent connectivity levels falling in the middle [24].

To summarize, across normal development, RSFC networks have been found to span longer distances in the brain and become increasingly segregated, resulting in both within-

and between-network efficiency. It appears that particular RSFC networks (i.e., involving the sgACC) are tied to specific developmental functions (i.e., emotional development). Gender differences have received little experimental attention but did appear to be present in studies that examined them [21]. Finally, anti-correlated networks have been reproduced in several studies as markers of more advanced, adult-like development [23, 24]. All of the studies reviewed here have had the limitation of cross-sectional designs and concerns about the impact of head motion on findings. Longitudinal examinations of developing RSFC networks are needed to definitively characterize changes across development.

Resting State Functional Connectivity Studies with Clinical Samples

Autism Spectrum Disorders

Current RSFC research comparing individuals with ASD and healthy comparison participants (with numbers of participants ranging from 20 to 39 for each group) has implicated RSFC abnormalities, including both abnormally high and abnormally low RSFC, in nearly every region of the cortex and the cerebellum [25, 26, 27, 28•].

Studies characterizing specific behavioral problems associated with ASD have largely focused on social and communication deficits. Assaf and colleagues found abnormally decreased RSFC between the precuneus and other DMN areas in ASD patients, compared with controls (n=16 per group) [29]. This atypical connectivity was associated with social and communication deficits [29]. A similar study found that increased RSFC between the posterior cingulate and temporal cortex was associated with social impairment (n=20 subjects with ASD; n=19 controls) [27]. Furthermore, Abrams and colleagues found that abnormally low RSFC between the temporal cortex and regions of the brain associated with reward was associated with severity of communication deficits among children with ASD (n=20 subjects with ASD; n=19 controls) [30••]. This finding suggests that communication deficits in ASD may be either the result of, or exacerbated by, reduced ability to associate social interaction with a sense of reward. This is important to consider in the treatment of ASD, as other, more salient, rewarding stimuli may be necessary to advance a patient’s social interaction skills. Indeed, this is a practice employed in an applied behavioral analysis (ABA) framework, which emphasizes the use of positive reinforcement in the promotion of social behaviors [31]. Further research examining RSFC before and after initiation of treatments would be of important clinical significance, as RSFC of these regions may normalize over time with interventions.

Regarding the developmental trajectories of RSFC among children and adolescents with ASD, findings have been inconsistent. One study found that relative to controls ($n=41$), ASD participants ($n=39$) had smaller increases in RSFC within the DMN over time [28•], while another found that group differences in DMN RSFC appeared to diminish with age ($n=40$ subjects with ASD; $n=40$ controls) [32]. Of note, these studies were both cross sectional, and overall functioning and treatment histories varied greatly in the participants in these studies. Future research should carefully consider the influence of these factors and implement longitudinal designs to better understand the developmental trajectory of RSFC in ASD.

Anxiety Disorders

Studies in this area, while few, have typically taken the approach of examining the association of pediatric anxiety severity with RSFC in healthy participants. Among typically developing children ($n=76$), Qin and colleagues found that anxiety was associated with increased RSFC between the amygdala and regions involved in emotion perception and regulation and attention [33]. Furthermore, these findings were specific to anxiety symptoms, as other symptoms, such as depressive symptoms, did not show a relationship to RSFC. Also among healthy youth ($n=67$), anxiety severity was related to increased DMN–insula RSFC [34]. A cross-sectional study found that life stress in infancy was associated with higher childhood cortisol levels and, later, with decreased amygdala–prefrontal RSFC. In turn, amygdala–prefrontal RSFC was inversely related to adolescent anxiety symptoms ($n=57$) [35]. Thus, anxiety symptoms in healthy samples implicate networks involving the insula, prefrontal cortex, and amygdala.

Roy and colleagues scanned adolescents with generalized anxiety disorder (GAD; $n=15$) and found abnormal amygdala RSFC between the medial prefrontal cortex, insula, and cerebellum, compared with findings in controls ($n=20$) [36•]. Furthermore, anxiety severity was associated with amygdala RSFC with the insula and superior temporal gyrus. Clearly, further research is needed to replicate these GAD findings and examine other unstudied pediatric anxiety disorders, such as separation anxiety disorder, social anxiety disorder, and specific phobias.

Mood Disorders

A larger body of literature has used resting state fMRI to examine the neural circuitry underlying mood disorders in children and adolescents. These studies have broadly implicated abnormalities within circuitry that has been shown to be relevant for processing emotions [37]. Specifically, this circuitry encompasses limbic regions such as the amygdala and

hippocampus, which are important for both immediate emotional experiences and emotional memory, and regulatory cortical regions such as the prefrontal cortex and the pgACC. Additional regions in this network include the sgACC, which has been strongly implicated in the pathophysiology of mood disorders through the use of several different types of imaging modalities and also postmortem studies [38–40], and the insula, which is known to be important for processing the emotional salience of an individual's experiences. Thus, abnormalities in this circuit could broadly impact emotional processing, resulting in mood states seen in both unipolar and bipolar depressive disorders.

Major Depressive Disorder

Several studies examining depressed youth have shown abnormalities in sgACC networks, although the pattern of findings has varied. In a small study of mostly medicated adolescents with major depressive disorder [MDD] ($n=12$) versus controls ($n=14$), Cullen and colleagues reported that depressed teens showed lower RSFC between the sgACC and a network comprising the dorsal ACC, several frontal and temporal regions, and the insula [41•]. These findings were corroborated in a sample of 36 children (aged 7–11 years), 17 of whom had a history of MDD [42]. However, other studies found greater RSFC between the sgACC and frontal regions in unmedicated adolescents with MDD ($n=23$) compared with controls ($n=36$) [43], and in adolescents/young adults with MDD ($n=18$) compared with controls ($n=20$) [40]. Furthermore, while Gaffrey and colleagues found greater RSFC between the sgACC and precuneus among children with histories of MDD [42], Connolly et al. found lower RSFC between the sgACC and precuneus in an adolescent MDD group [43]. The divergence of findings in the pattern of sgACC RSFC abnormalities across studies may stem from differences in methodological steps, sample characteristics (e.g., age, pubertal status, age at MDD onset, medication status, comorbidity), or general difficulty in replicability of RSFC findings. Larger studies are needed to clarify the RSFC of the sgACC in pediatric MDD.

Brain regions comprising the striatum (the caudate, putamen, and nucleus accumbens) are thought to play an important role in reward processing, which is known to be impaired in MDD [45]. Gabbay and colleagues examined RSFC centered around the striatum in medication-free adolescents with MDD ($n=21$) and healthy controls ($n=21$) [46•]. They reported that the MDD group showed greater RSFC between the striatal regions and the dorsomedial prefrontal cortex and ACC. They also reported a diverse set of connections that were associated with anhedonia [46•]. In contrast, Davey and colleagues found decreased ACC–caudate RSFC in older adolescents with MDD [44]. Although the directionality varied, both studies implicated abnormal frontostriatal neural

circuits in the pathophysiology of depression, especially with respect to anhedonic symptomatology.

The amygdala is another important brain region investigated in mood-disordered youth. This region is involved in the processing of negative emotion [47] and has consistently been implicated in mood disorders [48]. Luking and colleagues studied amygdala RSFC in a sample of children (aged 7–11 years) with either a history of preschool-onset MDD ($n=13$), a maternal history of MDD ($n=11$), both ($n=13$), or neither ($n=14$) [49]. They found that in comparison with low-risk children, the at-risk groups showed decreased negative amygdala connectivity in a network comprising cortical regulatory regions, but greater positive amygdala connectivity with a network of limbic regions. More recently, Cullen and colleagues examined amygdala RSFC in a large sample of unmedicated adolescents with MDD ($n=41$) versus healthy controls [50]. They found that adolescents with MDD showed lower amygdala RSFC with the hippocampus, parahippocampus, and brainstem, but increased amygdala–precuneus RSFC than controls. These findings partially overlapped with the Luking at-risk findings [49], suggesting that amygdala connectivity abnormalities may be present both in childhood and adolescence, before and after the onset of the disorder.

Bipolar Disorder

Three studies have examined RSFC in youth with bipolar disorder (BD). They used quite different approaches, and each revealed a different aspect of the aberrant RSFC. Dickstein and colleagues examined RSFC stemming from the dorsolateral prefrontal cortex, amygdala, and nucleus accumbens, and found a group difference with dorsolateral prefrontal cortex analysis, in which the BD group ($n=15$) showed greater negative RSFC with the right superior temporal gyrus, while controls ($n=15$) had positive RSFC in this circuit [51]. The authors noted that the abnormal frontotemporal circuit is also implicated in memory and learning, and could represent an underlying mechanism for the cognitive deficits involved in BD.

In a more recent paper, Wu and colleagues used an automated method to examine RSFC across the entire brain [52]. They found that in comparison with controls ($n=40$), youth with BD ($n=34$) had greater levels of involvement of the dorsal ACC within affective and executive networks, and greater widespread connectivity within a sensorimotor network. The authors speculated that the excessive involvement of the ACC in both affective and executive networks could explain the association of BD and poor academic performance.

Third, Xiao and colleagues recently studied regional homogeneity (ReHo) in 15 adolescents with BD and 15 healthy controls [53]. Relative to the controls, the subjects with BD showed lower ReHo in several cortical areas but greater ReHo

in several limbic areas. Furthermore, elevated limbic ReHo was correlated with manic symptoms. Thus, three papers, each using distinct methods, have reported cortical–limbic RSFC abnormalities. Caution must be taken in reading the BD literature, however, given the concern about likely differences between depressed, manic, and euthymic mood states [54]. Considering the difficulty in diagnosing these disorders in youth, additional work with larger, carefully characterized samples is needed.

Combined Mood and Anxiety Disorders

Depressive and anxiety disorders are often studied together because of their high comorbidity and their categorization as internalizing disorders [55]. Among children with a history of depression and anxiety ($n=30$), Sylvester and colleagues found reduced RSFC of the task-positive network, compared with findings in healthy controls ($n=42$) [56]. Another study found that maltreatment in childhood was associated with decreased RSFC between the hippocampus and the sgACC in both males and females with internalizing symptoms at the age of 18 years ($n=64$) [57••]. Decreased RSFC between the amygdala and the sgACC was also found but only in females [57••]. RSFC in this study was found to mediate the relationship between childhood maltreatment and later internalizing symptoms, suggesting that childhood maltreatment may lead to disrupted connectivity of the fear circuit, which may lead to increased levels of internalizing symptoms.

Attention-Deficit/Hyperactivity Disorder

Of all psychiatric disorders diagnosed in youth, ADHD has been the best studied, in terms of RSFC. A multi-site data-sharing effort, termed ADHD-200 [58•], has recently resulted in publications with very large samples. For example, ADHD brains ($n=757$) exhibited altered RSFC between the default network and ventral attention networks [59••]. Specifically, diminished anti-correlation was observed between the posterior cingulate cortex (DMN) and the anterior insula and supplementary motor area (ventral attention network). Additionally, the DMN was hypoconnected within-network and had abnormal interconnections between several other networks. This paper replicated similar DMN-related findings from other papers with smaller sample sizes [60, 61]. Given that these regions are involved in directing and sustaining attention, it is logical that they are found to be abnormal in a disorder with inattention as one of its hallmark symptoms.

Clinically meaningful applications of RSFC in ADHD have also begun to appear. Methylphenidate, a primary treatment for ADHD, has been found to influence RSFC of multiple regions, including the dorsolateral prefrontal, parietal, and visual cortices [62] and the DMN and task-positive network [63] in pediatric samples. Similarities between RSFC

networks have been identified between disorders with shared symptoms (e.g., autism and ADHD) [64], providing neurobiological substantiation for disorder-crossing traits. Clinically observed symptoms have been linked to specific RSFC networks. For example, youth with ADHD and high parent ratings of emotional lability have been found to have abnormal amygdala RSFC, even after accounting for hyperactivity [65]. Finally, RSFC has been used to test models to diagnose ADHD, using brain activity alone, although with mixed success [66, 67]. Research geared toward clinical applications of RSFC is still in its infancy, but it appears that such studies are likely to emerge in other psychiatric disorders affecting youth, as more publications emerge.

Psychotic Disorders

The use of fMRI in individuals with psychotic disorders is limited by the cognitive dysfunction associated with these illnesses, making performance on in-scanner experimental tasks difficult to interpret [68, 69]. Resting state fMRI circumvents the issue of in-scanner task performance and has proven to be a useful tool in schizophrenia research, revealing new information about the functional organization and connectivity of the brain [70–72].

There is increasing interest in studying individuals at ultra-high risk (UHR) for psychosis or those in their first episode of psychosis (FEP), as they consist of younger individuals with fewer confounding factors associated with chronically ill psychotic populations, such as antipsychotic drug exposure or medical comorbidities. Many studies in these early populations have examined RSFC of the DMN, finding abnormal coherence within DMN structures such as the medial prefrontal cortex, lateral temporal cortex, precuneus, posterior cingulate cortex, and parietal cortex [73–77]. Studies have also examined RSFC between DMN structures and other brain regions, finding abnormal connectivity with task-positive networks [74], as well as the dorsolateral prefrontal cortices [78]. Some of these studies have also examined inter-hemispheric connectivity, finding decreased RSFC in the frontal and temporal regions, and associations between aberrant connectivity and positive and negative symptoms, as well as cognitive dysfunction [73, 79].

A study by Lui et al. utilized resting state fMRI to investigate the effects of antipsychotic medication on regional and neural network function in treatment-naïve FEP subjects ($n=34$), examining RSFC both before and 6 weeks after the initiation of second-generation antipsychotic medication [80•]. The findings revealed that after this short duration of antipsychotic treatment, participants exhibited increased spontaneous regional neural activity in association with symptom improvement, as well as an attenuation of connectivity across widely distributed neural networks. These results may help explain the beneficial effects of antipsychotic medication,

hypothetically because of improvements in neurons' ability to function more synchronously with other regions. Importantly, this study highlights the promise that resting state fMRI may hold for strategic development of novel therapeutic agents, as well as for study of biomarkers of patient response to medication in psychotic illness [80•].

Conclusions

RSFC has been used to study the major child and adolescent psychiatric disorders, albeit with mixed conclusions. The field is still in its infancy, and all findings reviewed here require replication. However, as the methodology continues to advance, RSFC is a promising tool for populations that struggle to comply with tasks and is well suited to large-scale, multi-site, and longitudinal studies, such as those characterizing child and adolescent development. Despite these advantages, aspects of RSFC have been met with skepticism among some researchers [69, 81], as discussed in more detail below.

Limitation 1: What Are People Actually Doing at Rest? Interpretation of RSFC findings is subject to the limitation that investigators cannot be sure what their subjects are thinking about or feeling while they are resting. Of particular concern for studies with psychiatric populations, anxiety may be induced by the scanner experience and may be difficult to account for without a “control” task, as in task-based fMRI. Concerns have also been raised that research participants may sleep through scans and may not be aware of when they drift off, even if investigators inquire about this.

Limitation 2: Head Motion Two influential papers documented the serious impact of head motion during the MRI scan on RSFC results [82, 83]. Then, Satterthwaite and colleagues called the validity and replicability of previous developmental connectivity studies into question [84••]. They noted that in prior work on age-related increases in long-distance, within network connectivity and decreases in short-distance, between-network connectivity, the opposite pattern was seen for head motion. They reported that increased head motion is associated with younger age and that when connectivity analyses are conducted with rigorous correction of head motion effects, the developmental findings are still present but substantially tempered. That publication highlighted the importance of correcting for head motion in developmental studies of RSFC.

In summary, clinicians will likely encounter publications or presentations utilizing RSFC, an innovative fMRI technique. RSFC refers to spontaneous brain fluctuations, organized into functional communication networks, which are quantifiable when subjects are at rest. RSFC can reveal novel information

about how brain networks develop and how that development can go awry in various psychiatric disorders. The RSFC literature is still at an early stage, as illustrated by the fact that vast networks of abnormalities have been implicated for most disorders. Few findings have been replicated; this may be because many of the initial studies have included small samples and the methodologies to process and analyze the data have varied widely. RSFC is a technique that is quite susceptible to motion artifact, leading to some recent skepticism about the initial findings from pediatric studies, given the large degree of motion in children and adolescent participants. However, recent work has incorporated more robust techniques to address motion. Moving forward, studies with larger samples that incorporate uniform methods across studies will be most useful for advancing the field. There is strong interest in gaining insight into how RSFC changes across normal and abnormal development, thus longitudinal research is needed. RSFC is likely to continue to serve as an important neuroimaging modality as findings are reproduced, clinical interventions are tested, and analytic techniques improve.

Compliance with Ethics Guidelines

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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- Of importance
- Of major importance

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