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REVIEW

Resting state FMRI research in child psychiatric disorders

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Abstract Concurring with the shift from linking functions to specific brain areas towards studying network integration, resting state FMRI (R-FMRI) has become an important tool for delineating the functional network architecture of the brain. Fueled by straightforward data collection, R-FMRI analysis methods as well as studies reporting on R-FMRI have flourished, and already impact research on child- and adolescent psychiatric disorders. Here, we review R-FMRI analysis techniques and outline current methodological debates. Furthermore, we provide an overview of the main R-FMRI findings related to child- and adolescent psychiatric disorders. R-FMRI research has contributed significantly to our understanding of brain function in child and adolescent psychiatry: existing hypotheses based on task-based FMRI were confirmed and new insights into the brain's functional architecture of disorders were established. However, results were not always consistent. While resting state networks are robust and reproducible, neuroimaging research in psychiatric disorders is especially complicated by tremendous phenotypic heterogeneity. It is imperative that we overcome this heterogeneity when integrating neuroimaging into the diagnostic and treatment process. As R-FMRI allows investigating the richness of the human functional connectome and can be easily collected and aggregated into large-scale datasets, it is clear that R-FMRI can be a powerful tool in our quest to understand psychiatric pathology.

Keywords Resting state FMRI · Functional connectivity · Child- and adolescent psychiatry · ADHD · ASD · MDD · Heterogeneity · Imaging

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Transcending localization

The year 2012 marked the 20th anniversary of the first published reports on functional magnetic resonance imaging (FMRI) [1–3]. While significant progress has been made in imaging sequences, stimulation paradigms and analysis techniques, the basic principle of FMRI research has remained the same. By stimulating a participant, for instance by presenting a visual stimulus, researchers attempt to induce changes in neuronal functioning. FMRI is not capable of directly capturing neuronal activity, but

changes in neuronal functioning are accompanied by changes in blood flow and oxygenation level of blood delivered to active neurons [4]. Accordingly, changes in the blood's oxygenation level can be captured by MRI sequences, due to a difference in magnetic properties of oxy- and deoxyhemoglobin. For over 20 years, measuring the blood oxygenation level dependent (BOLD) signal using carefully designed FMRI experiments has enabled neuroimagers to locate specific brain regions implicated in specific cognitive processes. However, transcending models of local processing, the FMRI community is now shifting its interest from localizing functions to studying how activity observed for various regions of the brain is integrated into functional brain networks [5–7].

Concurring with the shift towards studying network integration, resting state FMRI (R-FMRI) has become an important tool for delineating the functional network architecture of the brain. R-FMRI images a participant while simply "laying still" *or* "resting", thereby focusing on the brain's spontaneous activity. Subsequent R-FMRI analyses describe so-called resting state networks (RSN; see Fig. 1) as defined by patterns of temporal synchrony among brain regions [8–10]. These RSN closely resemble networks observed during task performance [11], enabling researchers to discern the brain's generic, task-independent functional architecture without a need for specialist task paradigms.

A major advantage of R-FMRI is that the full gamut of networks constituting the functional architecture of the brain can be studied within a single R-FMRI dataset. RSN exhibit high test–retest reliability between and within subjects [12–14], as well as high reproducibility among labs [15]. Additionally, the clinical applicability of R-FMRI is much enhanced by the minimal participant compliance required in contrast to the need to learn complex task paradigms. This makes R-FMRI ideally suited for studies across the lifespan and for imaging clinical cohorts (e.g., ADHD, autism, schizophrenia, Alzheimer's disease) that may also include patients with low IQ.

Fueled by the ease-of-use of R-FMRI, the neuroimaging community's shift towards studying network integration has influenced FMRI research in clinical populations, especially within psychiatry. Many disorders are no longer approached as disorders of brain function in isolated regions but rather as a breakdown of communication and integration among large-scale functional brain networks [16, 17].

Methods and techniques

Functional connectivity is the most common analytic approach to study network integration. Specifically, functional connectivity aims to capture the synchronicity of the BOLD signal across various regions of the brain, or, in other words, assess large-scale patterns of coherent signals [18]. One application of functional connectivity is to assess the influence of experimental manipulations on signal

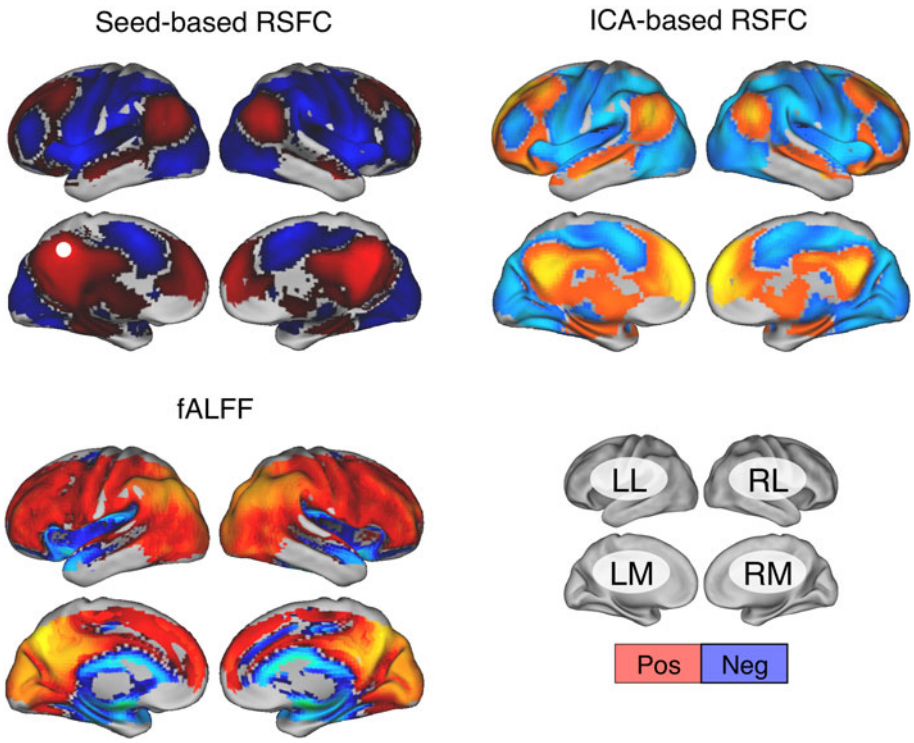

Fig. 1 Resting state networks. Resting state functional connectivity as revealed by three common analysis techniques: seed-based resting state functional connectivity (RSFC) of a seed in posterior cingulate cortex (*white dot*); the default mode network identified using independent component analysis (ICA); and amplitude of low frequency fluctuations (ALFF). *Pos* positive functional connectivity, *Neg* negative functional connectivity, *LL* left lateral, *RL* right lateral, *LM* left medial, *RM* right medial. (Figure adapted from [15]). The illustrated analysis techniques are reviewed in the "Methods and techniques" section of this manuscript

synchronicity. Typically applied to task-based FMRI data, this approach is the core of a psycho-physiological interaction analysis (PPI) [19] or dynamic-causal modeling (DCM) [20].

In R-FMRI data, functional connectivity simply captures the synchronicity of spontaneous brain activity. Popular approaches included assessing signal synchronicity between regions of interest or grouping voxels based on the synchronicity of their BOLD signal over the course of an R-FMRI scan. Yet, despite the popularity of R-FMRI, little consensus exists regarding optimal parameters and settings to be used during image analysis or during scanning itself. Here, we briefly report on current methodologies before continuing with an overview of R-FMRI findings in child- and adolescent psychiatric populations. Table 1 provides short explanations for commonly used analysis terminology. Terminology explained in the table is indicated by ** in the text.

Scanning protocol

Although R-FMRI can be implemented using echo-planar imaging (EPI) protocols that are commonly used in task-based studies, little is known about the impact of scanning parameters on obtained connectivity measures. Typically, R-FMRI scans are 5–10 min long. A scanning length of 6 min, with a typical whole-brain volume repetition time (TR**) of 2–3 s, seems sufficient to obtain reliable estimates of connectivity strength [21], but a length of 8–10 min (with TR = 2 s) is recommended. Longer scanning times provide better signal-to-noise ratio and increase the available degrees of freedom needed for high-dimensional decompositions [11, 22]. Of note, current developments in MRI sequences now allow imaging the whole brain with much shorter TR (e.g., 400 ms), resulting in (R-)FMRI data with a much greater temporal resolution.

Next to scanning parameters, the precise experimental settings during an R-FMRI scan vary. There is no standardization of instructions (e.g., 'just relax' vs. 'try not to think about anything in particular') and scans can be recorded with eyes open, closed or fixated. Overall, different paradigms yield similar results, though for instance eye-status affects connectivity measures, e.g., fixation and eyes open conditions yield stronger correlations compared to eyes closed recordings [21, 23]. As eyes open conditions, in addition, provide better prevention against participant drowsiness or even sleep, we typically recommend fixation or eyes open recordings over eyes closed recordings. Furthermore, R-FMRI measurements are influenced by prior cognitive effort [24–26], suggesting that preceding task-related activity may linger into subsequent resting episodes. Accordingly, the position of an R-FMRI scan within a longer scanning session should be carefully considered. Ideally, R-FMRI scans are purposefully positioned early in an MRI session rather than added at the end of the MRI session to fill remaining scan time.

Table 1 Commonly used R-FMRI analysis terminology

Voxel	3D cube within a brain image, equivalent to a pixel in a digital photograph
TR	Repetition time: the amount of time required to acquire one (full) brain volume (or in MRI technical terms: the amount of time between successive excitations of the same image slice)
Time course or time series	A series of measurements representing BOLD activity (of a voxel) over time
Preprocessing	Any manipulation of the data to decrease noise and increase signal strength applied before a model of interest is estimated
Slice timing correction	Time-shifting or interpolating all slices in a volume to line up with a reference slice to correct for the fact that not all slices of a functional volume are sampled at exactly the same time
Realignment/ motion correction	Reorienting of all functional images to the same position to correct for motion during scanning
Grand mean scaling	Rescaling all participant time series to a common mean to account for between participant data-offsets due to the relative magnitude of MRI data
Temporal filtering	Removing data oscillating at frequencies that are typically considered to represent noise
Frequency aliasing	Blending of signals from different sources in the frequency domain due to signal undersampling as a result of typically slow TR (of the order of 1–3 s) relative to e.g., physiological noise sources such as heartbeat and respiration
Spatial smoothing	Blurring of the functional images in the spatial domain. Each voxel's intensity is replaced with a weighted average of its own intensity and the intensity of its neighboring voxels by means of a Gaussian kernel in order to increase signal-to-noise characteristics
Nuisance regression	Removal of a time series associated with a noise source (e.g., CSF signal) from the data through linear regression. Processing is then continued on the residuals of this regression
Single-subject analysis	Analysis of an individual subject's dataset or an individual session
Group-level analysis	Analysis combining results from single-subject analysis across multiple subjects

Image preprocessing

Most preprocessing** steps for the analysis of task-based BOLD fMRI data can also be applied to R-FMRI data, e.g., discarding first volumes to allow for magnetic field

stabilization, motion correction through realignment**, grand mean scaling** and spatial smoothing** [21]. Different opinions exist regarding temporal filtering**. A typical assumption in R-FMRI analyses is that spatial information in the R-FMRI signal is driven by low frequency fluctuations (<0.1 Hz), with cardiac, respiratory and other types of noise dominating higher frequency ranges [27]. Accordingly, most studies implement a band-pass filtering approach sparing frequencies between 0.001 and 0.1 Hz with the intention to reduce noise and other unwanted signals. However, recent studies suggest that the higher frequency range should not be ignored [28, 29]. In addition, due to frequency aliasing**, it is impossible to fully remove noise related to cardiac and respiratory signal from FMRI data through temporal filtering. A better approach is to monitor these signals during data acquisition and subsequently remove them from the data (e.g., as implemented in RETROICOR) [30].

Next to cardiac and respiratory noise, it is typical to account for noise related to movement, white matter and cerebro-spinal fluid signal by means of nuisance regression** [21]. In contrast, including the global signal (mean signal across all voxels**) as a nuisance regressor is highly controversial. Most studies include the global mean signal (GMS) to correct for non-neuronal physiological noise; however, this method will bias towards finding negative correlations between networks [31]. Whether global signal regression (GSR) induces false negative correlations between networks or enhances present negative correlations is subject of debate [21, 30, 32–38].

Another problematic issue is the impact of in-scanner head motion on various measures of resting state functional connectivity, even after applying common methods for motion correction [39–43]. This can be particularly problematic when examining developmental changes in youth since head motion and age of the participant are highly related [40]. Denoising by means of independent component analysis (ICA) can be added to decrease noise, including the impact of motion [44], yet this method depends on identification of noise by the experimenter (for more on ICA see below). Recent evidence showed that an improved preprocessing pipeline substantially reduced the effect of head motion on R-FRMI [41]. However, motion effects cannot be completely removed and questions remain on the validity of the approach in light of the temporal characteristics of the R-FMRI signal [42, 45].

Computing functional connectivity

Over the past decade, methods available for defining functional connectivity using resting state FMRI data have increased exponentially. A wide variety of approaches now exists, each with its own strengths and weaknesses. We describe the most commonly applied methods, seed-based functional connectivity and independent component analysis, and briefly touch on alternative approaches for analyzing resting state data.

Seed-based functional connectivity

First applied by Biswal and colleagues in 1995 [8], seed-based functional connectivity assesses signal synchronicity using regions of interest or seeds. The BOLD signal over time is extracted for one or more "seeds". Next, these time series data are entered in a correlation analysis or as a regressor in a general linear model (GLM) to calculate the whole-brain voxel-wise functional connectivity maps indexing the covariance of each voxel's time series with the time series of the seed [18, 46]. In addition to whole-brain analyses, seed-based functional connectivity can also be calculated between a collection of seeds.

Seed-based functional connectivity is explicitly model-based, since the a priori selection of one or more seeds is necessary. Seed selection should be hypothesis driven and can for instance be based on existing literature or an FMRI localizer. A key feature of seed-based functional connectivity is its straightforward interpretability [46]: it exposes those regions that most strongly correlate with the seed signal. As such, many groups apply seed-based functional connectivity to study the functional connections of a multiplicity of seeds. However, due to the focus on a limited number of seeds, additional outcomes might remain uncovered and findings may be biased.

Independent component analysis

A second common approach to study functional connectivity is independent component analysis (ICA). ICA is a blind-source separation method that can be applied to many types of data and was first applied to R-FMRI in 2003 [47]. ICA decomposes the data into a number of independent components, based on the assumption that the data consist of a mix of independent signals from various independent sources. Applied to FMRI data in the spatial domain, ICA returns several maximally independent spatial maps (components, see Fig. 2), by grouping voxels with similar time courses** [48].

Although no initial assumptions need to be made regarding regions of interest, ICA requires the number of components it should decompose to be specified or estimated. Some toolboxes implement methods for automatic dimensionality estimation (e.g., MELODIC), but more commonly the user decides on the number of components. As a consequence, a plethora of numbers is used, ranging from the typical 20–30 to 150 and more [49]. A higher number of components might decompose networks into

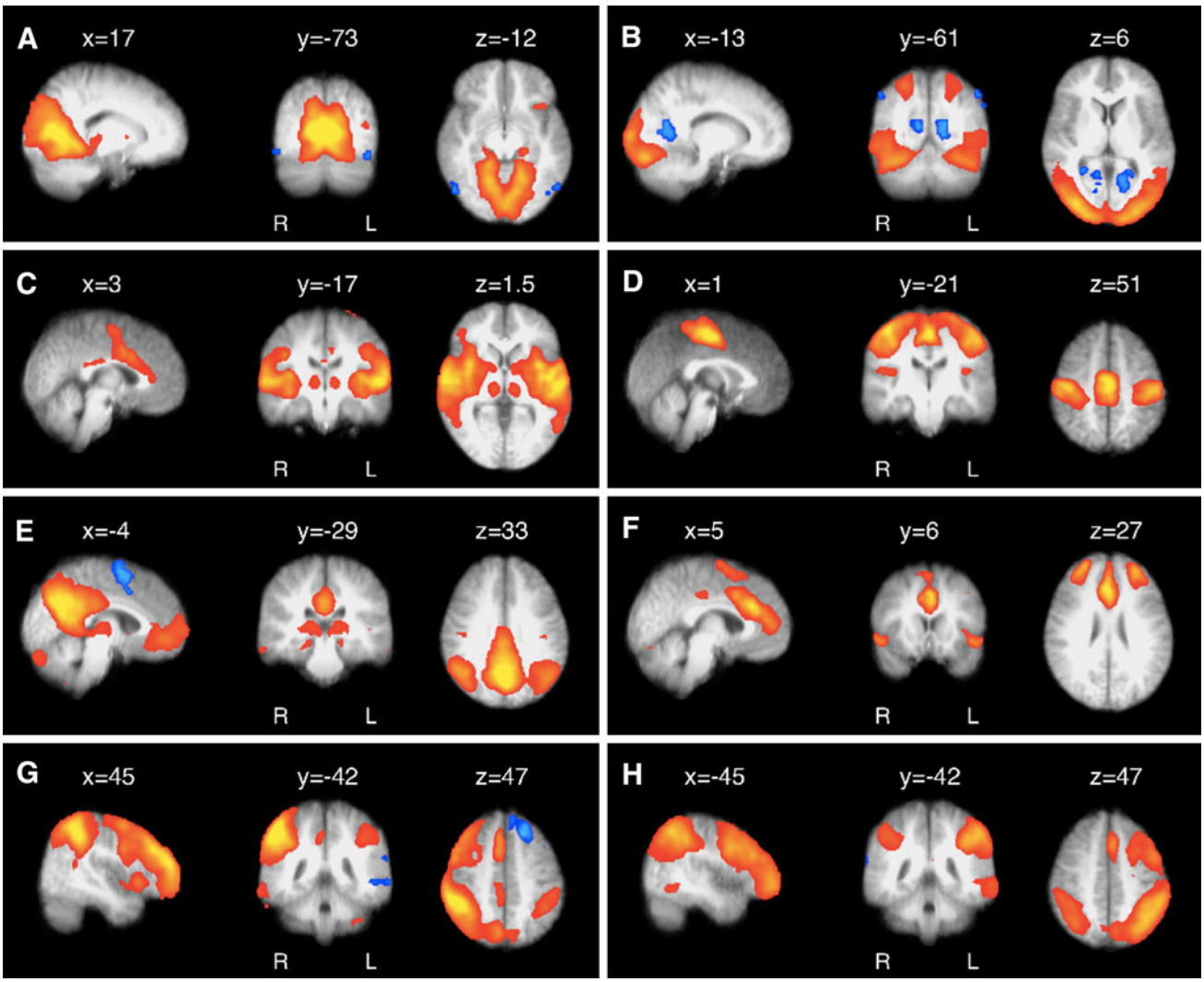

Fig. 2 Eight common and consistent RSNs identified by ICA. **a** RSN located in the primary visual cortex; **b** extrastriate visual cortex; **c** auditory and other sensory association cortices; **d** the somatomotor cortex; **e** the 'default mode' network (DMN); **f** a network implicated in executive control and salience processing; and (G,H) two right- and left-lateralized fronto-parietal RSNs spatially similar to the bilateral dorsal attention network and implicated in working memory and cognitive attentional processes (reprinted with permission; Cole et al. [18], Beckmann et al. [9])

multiple subnetworks. Furthermore, both relevant components as well as noise components are extracted, posing difficulties on component identification and interpretation. Noise components can be removed from the data. Typically, the user needs to identify components to remove, although automated classification techniques are being developed [50].

Unlike seed-based functional connectivity, where voxelwise regression coefficients or correlation coefficients are forwarded from single-subject analysis** to group-level analyses**, a group-level analysis of ICA components is hampered by the fact that components corresponding across subjects have to be identified. Different methods for defining or extracting corresponding components have been suggested, including template matching [10, 51, 52], back reconstruction [53] and dual regression [54].

ICA is typically applied in the spatial domain, but can also be applied in the temporal domain to identify temporally independent functional networks [55]. Until recently, application of temporal ICA in FMRI has been impractical due to the limited number of time points (and the associated limited number of temporal degrees of freedom) available in a typical FMRI scan. One would have to scan for hours to obtain sufficient time points. However, technical advances now allow collecting data with faster volume repetition times, resulting in improved temporal resolution (e.g., 500 ms vs. 2 s. per volume, effectively quadrupling the temporal resolution). Applying temporal ICA to data from such a fast FMRI sequence,

Smith and colleagues [55] described several temporal functional modes within spatially overlapping functional networks. Although promising, future research is required to optimize this technique and provide a better understanding of its implications.

Other analysis techniques applied to R-FMRI data

Next to seed-based functional connectivity and ICA, various other methods for analysis of resting state FMRI data exist including amplitude of low-frequency fluctuations (ALFF), regional homogeneity (ReHo) and graph theoretical approaches. ALFF indexes the strength of lower frequencies in the BOLD signal. The employed frequency band commonly ranges from 0.01 to 0.1 Hz [56, 57]. However, ALFF might be affected by cerebral vascular and respiratory noise. Furthermore, recent work suggests that frequencies above 0.1 Hz also contribute to resting state functional connectivity [28, 29].

ReHo focuses on local connectivity by measuring the functional coherence of a certain voxel with its neighboring voxels using "Kendall's coefficient of concordance (KCC)" [58]. ReHo is based on the hypothesis that neighboring voxels exhibit similar temporal properties. A drawback of this approach is that it is highly influenced by the degree of smoothing and measures only local coherence.

Graph theory has already contributed to many different research areas and is now commonly applied to R-FMRI analysis as well [59]. Graph theory measures try to capture the brain's architecture by considering regions of interest (ROIs) as nodes and functional connections between the nodes as edges. By subsequently characterizing properties of those nodes and edges, functional brain networks can for instance be described in terms of efficiency and modularity [59, 60]. However, implicitly based on seed-based connectivity outputs, graph theory is dependent on the appropriate definition of network nodes, although voxel-wise implementations are beginning to emerge [61].

Above we provided a short overview of a variety of approaches available for the analysis of R-FMRI data. Each method has its advantages and disadvantages and the method of choice depends on the research question at hand. Despite this variety of paradigms and methods, resting state analyses have been shown to generate reproducible and reliable results [12–14, 61, 62]. Nevertheless, future research is necessary to optimize the resting state scanning paradigm and preprocessing pipeline, as well as to advance techniques for further analysis of R-MRI data. An area of particular interest is the dynamic nature of functional connectivity. All methods described above consider functional connectivity to be a static phenomenon. However, recent studies are beginning to highlight the dynamic nature of functional connectivity, as even within short time-intervals new functional associations can be formed or existing ones can be altered [63–65].

Resting state functional connectivity in child and adolescent psychiatry

The limited participant compliance required during R-FMRI scanning, as well as its ability to probe multiple functional systems using the same dataset, makes R-FMRI ideally suited for imaging clinical populations including children and adolescents with psychiatric disorders. Further supported by continuing methodological advances, many groups have recently started to apply R-FMRI to examine brain function in child and adolescent psychiatric disorders. R-FMRI has been mostly used to identify differences between patients and controls as well as to correlate inter-individual differences in resting state functional connectivity to inter-individual differences on clinical measures. Most studies focused on attention-deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), or major depressive disorder (MDD). Here, we review key findings and implications (see the supplement for literature search criteria). A detailed summary of included literature can be found in Table S1.

Resting state functional connectivity in attention-deficit hyperactivity disorder

ADHD is the most prevalent neurodevelopmental psychiatric disorder and is clinically characterized by symptoms of inattention, hyperactivity and impulsivity [66]. Task-based FMRI studies have documented various ADHD-related abnormalities in cognitive brain functioning [67, 68]. Most consistently reported are reduced activations in prefrontal cortex (PFC), anterior cingulate cortex (ACC), striatum, and cerebellum [67–70]. Although these FMRI studies suggest a neurobiological basis of ADHD, the specific mechanisms underlying atypical brain function in ADHD remain poorly understood.

The first studies examining R-FMRI in youth with ADHD focused on hypotheses of fronto-striatal-cerebellar malfunction [71, 72]. One particular region of interest has been dorsal ACC (dACC). Various task-based FMRI studies have related dACC dysfunction to behavior (inattention, impulsivity, and hyperactivity) that is typical of ADHD (for reviews see [73–75]). Using dACC as a region of interest in resting state functional connectivity studies has suggested aberrant connectivity with subcortical and cerebellar structures [72], and with regions of the default mode network (DMN) [76]. A key role for ACC dysfunction in ADHD is further supported by many other

R-FMRI studies reporting on aberrant ACC functional connectivity in ADHD [56, 71, 77–81]. Next to ACC, aberrant functional connectivity in youth with ADHD was most frequently demonstrated in relation to the DMN [71, 76, 78–80, 82–86]. In task-based FMRI studies, the DMN has been reported to show decreased activity during task performance [87]. This network underlies self-referential cognitive processes which are typically suppressed during attentionally demanding tasks [88]. According to the default mode hypothesis of ADHD, impaired task-related suppression of the DMN contributes to the disruption of cognitive performance in ADHD [88]. This ADHD DMN hypothesis has not only been confirmed by R-FMRI results but has also been strengthened by a recent meta-analysis of task-based FMRI studies in ADHD [67]. This meta-analysis demonstrated increased activation of the DMN in ADHD subjects during cognitive tasks, in addition to decreased activation of the fronto-parietal and ventral attention network.

Response inhibition and impulsivity are considered a hallmark of ADHD [89]. Response inhibition is thought to be governed by inferior frontal gyrus (IFG) [90]. Both structural and functional MRI studies have related IFG abnormalities to deficits in response inhibition in ADHD (for review see [91]). Accordingly, aberrant resting state functional connectivity of IFG has been reported in boys with ADHD [56, 71, 84]. Impulsivity, on the other hand, has been linked to the reward system, including orbitofrontal cortex (OFC) and ventral striatum (e.g., for review see [92]). Several studies have reported aberrant functional connectivity for these regions [e.g., 80, 85]. Costa Dias and colleagues [85] for instance reported that greater impulsivity as indexed by steeper delayed-reward discounting was correlated with ADHD-related increases in functional connectivity between ventral striatum and frontal regions. Further, widespread patterns of ADHD-related atypical striatal functional connectivity including connectivity with frontal regions have been reported [78, 86, 93], as well as correlations between measures of inhibition and striatal connectivity [78].

Moreover, evidence of abnormal functional connectivity between striatum and cerebellum [86] as well as aberrant functional connectivity within the cerebellum in ADHD has been described [56, 77, 80]. The cerebellum is thought to modulate fronto-striatal function [94] and an increasing number of studies indicates both structural and functional cerebellar abnormalities in ADHD [95–97]. In addition, decreased functional connectivity density (FCD) in cerebellum correlated significantly with inattention and impulsivity/hyperactivity in children with ADHD [80]. Finally, An and colleagues [98] recently demonstrated that an acute dose of methylphenidate normalized aberrant fronto-parieto-cerebellar connectivity in boys with ADHD.

Considerable R-FMRI evidence thus supports atypical functional connectivity in fronto-striatal-cerebellar circuitry and the DMN in youth with ADHD. Furthermore, symptom severity in children and adolescents with ADHD was found to correlate with the discovered abnormalities in these regions [80, 86]. Findings suggesting involvement of other brain circuits in ADHD are, however, often overlooked [99]. These findings include atypical functional connectivity of the medial occipital cortex/lingual gyrus [71, 76–78, 82, 84, 100] and the motor system [56, 81, 98]. In spite of reported ADHD-related aberrant functional connectivity, its underlying causes remain unclear. Some studies have suggested that typical development of functional connectivity might be delayed in youth with ADHD [76, 101].

Of note, recent investigations into the effects of movement-related artifacts on R-FMRI findings [39–42] have questioned the validity of R-FMRI results in movement-prone populations such as children with ADHD. Therefore, caution is warranted when interpreting the findings above, although future research is needed to assess the extent of possible interactions between ADHD diagnosis and movement-related artifacts during scanning.

Resting state functional connectivity in autism spectrum disorders

Autistic disorder, Asperger disorder, and pervasive developmental disorder not otherwise specified (PDD-NOS) are referred to as autism spectrum disorders (ASD). These disorders are classified as pervasive disorders and characterized by deficits in social communication and interaction, as well as restricted, repetitive and stereotyped behavior, interests, and activities [66]. Task-based FMRI studies have repeatedly associated these characteristic behaviors with atypical activity of various brain regions, including the mirror neuron system [102] and frontal and insular cortical regions [103]. In addition, Just and colleagues [104] described decreased functional connectivity of language-related brain regions in ASD. Accordingly, they hypothesized that ASD arise as a consequence of global under-connectivity. Some studies suggest that in addition to global under-connectivity, local hyper-connectivity is present as well [105]. As R-FMRI allows assessing multiple networks at once, it is ideally suited to further investigate both hypotheses in ASD youth.

Supporting the global under-connectivity hypothesis of ASD, decreased resting state connectivity of DMN structures was reported for youth with ASD compared to controls [106–112]. Patients with ASD exhibited altered development of DMN connectivity with age [109]. Furthermore, DMN connectivity was correlated with measures of social and communication skills [106–108, 110] and

with measures of repetitive behavior and interests [106]. While these studies suggested global under-connectivity of the DMN in ASD, under-connectivity was also reported in functional connectivity networks related to social proficiency. Gotts and colleagues [113] demonstrated widespread reduced functional connectivity in youth with ASD of regions related to social and emotional processing, including ventromedial PFC, amygdala, hippocampus and temporal regions. Decreased functional connectivity of limbic regions was associated with increased social symptom severity. Of note, while most studies focused on under-connectivity, DMN hyper-connectivity was also reported [108].

In light of reported language-related impairments in ASD, toddlers with ASD were found to exhibit weaker interhemispheric connectivity in the posterior parts of the IFG and superior temporal gyrus (STG), commonly referred to as Broca's and Wernicke's area, respectively [114]. Moreover, even in these young children, interhemispheric connectivity strength was positively correlated with language ability and negatively with autism severity. In a ReHo study, differences between ASD and control subjects were found in IFG and STG as well [115].

Some studies also implicated increased connectivity of subcortical structures supporting local hyper-connectivity and increased subcortical-cortical connectivity in the psychopathology of ASD [112, 116, 117]. In addition, increased functional connectivity between striatal subregions and various associative and limbic cortices previously associated with ASD, including right STG and insular cortex, was demonstrated [116].

Finally, accumulating evidence suggests that motor impairments present in ASD relate to social and communicative deficits and may reflect abnormal connectivity of brain networks underlying motor control and learning [118, 119]. Accordingly, Nebel and colleagues [120] investigated the functional organization of the primary motor cortex (M1) by parcellating M1 based on patterns of functional connectivity. Functional organization of M1 was different in children with ASD in regions corresponding with the upper and lower limbs. The authors suggested that this might be due to a delay in functional specialization in the motor cortex in ASD.

Recently, the Autism Brain Imaging Data Exchange (ABIDE) consortium analyzed R-FMRI data from 360 males with ASD and 403 male control subjects [112]. Both hypo- and hyper-connectivity were detected in males with ASD. However, in line with previous findings, global hypo-connectivity dominated, particularly for cortico-cortical and interhemispheric functional connectivity whereas hyper-connectivity was limited to connections with subcortical regions. In addition, seed-based correlations confirmed previous findings of decreased functional connectivity between anterior and posterior regions of the DMN.

To summarize, altered resting state functional connectivity was demonstrated in young ASD patients and correlated with (social) symptom severity, suggesting a key role for aberrant functional connectivity in the development of ASD symptoms. Yet, there is marked heterogeneity in the specific networks implicated in ASD pathology. Overall R-FMRI results provide support for the global under-connectivity hypothesis of ASD, although evidence suggesting short-range hyper-connectivity, predominantly in subcortical structures, has also been provided.

Resting state functional connectivity in major depressive disorder

Major depressive disorder (MDD) can be characterized by severely negative mood and/or loss of interest and pleasure for a longer period of time [66]. In line with evidence from adults, an important feature of pediatric MDD is thought to be emotional dysregulation. Neuroimaging studies implicate the fronto-limbic neural circuitry associated with emotion regulation in the pathophysiology of MDD. Imbalanced activity between frontal 'control' regions and limbic 'emotion' regions, with a key role for subgenual ACC [121, 122], is hypothesized to result in emotional dysregulation in MDD (for review see [123]).

Compared to healthy controls, adolescents with MDD exhibited reduced functional connectivity between the subgenual ACC and a network of cortical areas including frontal and temporal regions [124]. Aberrant functional connectivity of both subgenual ACC and posterior cingulate cortex (PCC) was demonstrated in children with a history of preschool depression [125, 126]. Moreover, increased functional connectivity between PCC and perigenual ACC was associated with decreased levels of current emotion regulation and coping in these children. Support for involvement of fronto-limbic circuitry comes from studies reporting atypical resting state connectivity of amygdala, insula and prefrontal cortex in youth with MDD [127–129]. Increased depression duration was associated with increased amygdala-pre/post central gyrus connectivity strength [128].

Resting state functional connectivity in other child psychiatric disorders

R-FMRI-based functional connectivity research in child and adolescent psychiatric populations has focused on ADHD, ASD and MDD. In addition, some studies have examined functional connectivity in pediatric obsessive compulsive disorder (OCD) and pediatric bipolar disorder (BD).

Although the exact diagnostic criteria for pediatric BD are subject to debate [130], BD is characterized by episodes of extreme and impairing changes in mood, thinking and behavior [66]. Both volumetric and task-based functional MRI studies have implicated altered fronto-temporal function in pediatric BD [131–136]. Accordingly, Dickstein and colleagues [137] reported decreased resting state functional connectivity between right STG and both left SFG and middle frontal gyrus, as well as increased functional connectivity between right STG and right parahippocampal gyrus. Xiao and colleagues [138] reported increased local connectivity—indexed by ReHo—in hippocampus, right ACC, right caudate and left parahippocampal gyrus in pediatric BD patients. Decreased local connectivity was observed in precuneus, precentral gyrus, superior frontal gyrus (SFG), right OFC, and right STG. Local connectivity of SFG, hippocampus and ACC was correlated with manic symptoms.

OCD, on the other hand, is characterized by distressing obsessions and compulsions that hinder daily life functioning [66]. The medial frontal cortex (MFC) and ACC have been related to performance monitoring and their hyperactivity has been suggested to trigger repetitive thoughts and behaviors in OCD [139, 140]. Patients with OCD showed decreased ventral MFC-PCC connectivity [141] as well as decreased functional connectivity between striatal regions and regions in ACC and MFC [142]. Decreased left dorsal striatum-rostral ACC connectivity was associated with increased OCD severity.

Finally, a limited number of studies examined R-FMRI in other child psychiatric disorders including pediatric Tourette syndrome [143], internet addiction [144], internet gaming addiction [145] and generalized anxiety disorder [146].

Resting state functional connectivity and diagnostic classification

Next to describing the functional architecture of (child) psychiatric disorders, researchers have enthusiastically started exploring R-FMRI as a tool to characterize individual patients and clinical heterogeneity in psychiatric disorders. One extensive, grass-roots initiative was the ADHD-200 global competition [147] where researchers were challenged to predict childhood ADHD diagnosis using over 900 R-FMRI datasets aggregated from eight international imaging centers. A special issue in Frontiers in Systems Neuroscience [147] bundles methods and results from different competitors (see http://www.frontiersin.org/Systems_Neuroscience/researchtopics/Collaborative_efforts_aimed_at/725). Next to the enthusiasm of researchers for disease classification approaches (over 20 teams participated), the competition results highlighted the complexity of this approach. Maximal predication accuracy for unlabeled datasets was 60.51 %, well above the 33 % chance-level (three-class classifier), but far from clinical usability. Although most competitors attained high levels of specificity, they reached only low levels of sensitivity. In other words, most methods were overly cautious, classifying many ADHD cases as controls (low sensitivity), but when a case was identified as having ADHD this classification was most often correct (high specificity). Accordingly, researchers are beginning to accept that individual patient classification based on the brain's functional architecture alone might not be feasible. Instead, further characterizing participants beyond their functional brain architecture by including behavioral data, structural brain measures, and genetic information could improve our ability to support the diagnostic process.

Future directions

Both its ease-of-use and the distributed nature of resulting network readouts have led to common inclusion of R-FMRI in clinically oriented FMRI protocols. Accordingly, in recent years, R-FMRI studies have confirmed prior hypotheses as well as provided new insights into the brain's functional architecture underlying child and adolescent psychiatric disorders. However, results were not always consistent. As the R-FMRI field expands rapidly, it is characterized by methodological heterogeneity. Studies increasingly report aberrant functional connectivity within and between various networks of interest, and with a vast variety of metrics. Unfortunately, such scattered diagnostic findings rarely translate into clinically useful biomarkers. Therefore, to avoid 'blobology' at the network level, we need approaches that are sensitive to subtle variations, inclusive in what they capture, specific when distinguishing subgroups, and well validated for clinical use.

One roadblock to achieve integrated approaches is current debate over best practices in R-FMRI preprocessing. Should global signal correction be adopted or avoided? How to best deal with movement-related artifacts? While various approaches have been proposed for global signal correction [21, 30, 32–36] and for dealing with movement-related artifacts [39–42] debate continues over their implementation, usefulness and impact on R-FMRI readouts [43, 148]. The possible influence of movement-related artifacts on R-FMRI findings, in particular, warrants increased attention as movement-related artifacts have been shown to mimic developmental or disorder related findings. As increased scientific rigor in FMRI research should be one of our immediate goals for the future [7], resolving these unsettled issues should be high on any (R-)FMRI methodologist's priority list. Likewise, replication

of findings across processing techniques and methodologies will be our best defense against isolated clinical findings.

In the past decade, neuroimaging shifted its focus from localizing symptoms in certain brain areas to approaching psychiatric disorders from a network perspective. Accordingly, the desire to localize should be avoided when trying to understand the underlying functional architecture of a disorder. Indeed, it seems unlikely that aberrant functional connectivity reported for a network of interest (e.g., default mode) is limited to that network only, as within the connectome [149] disturbance of network A will impact network B. Therefore, clinical findings tied to certain networks should be regarded in light of the restricted hypotheses and focused investigations that led to them rather than as the 'network of origin' for a particular disorder. As such, studies reporting on isolated aberrant functional connectivity miss the opportunity to assess their populations in terms of a communication breakdown between integrated networks. However, it should be noted that methods for such integrated network analysis are an area of recent and active development.

Characterizing participants based on an integrated assessment of the brain's functional architecture (including brain structure and participant behavior) will extend our ability to stratify participants beyond simple diagnostic categories. Psychiatric neuroimagers are increasingly confronted with tremendous phenotypic heterogeneity, as it is clear that even within diagnostic subgroups patients are not alike. While patients might exhibit similar behavioral characteristics, they could have markedly different underlying biology. Moreover, even within behaviorally defined diagnostic subcategories, patients can be divided into behaviorally distinct subgroups [150]. In addition, next to distinct subgroups within disorders, phenotypically distinct subgroups can transcend diagnostic categories. Accordingly, discovery science studies are shifting their methodology from comparing diagnostic subgroups to detecting and characterizing phenotypic subgroups using data-driven approaches (e.g., community detection, clustering) or data-mining [e.g., 151]. An example is the interest within the imaging community to develop 'growth curves' indexing functional connectivity development [e.g., 148, 152]. The associated idea is that, just as for typical growth curves available for weight and height, deviation from one's developmental curve could suggest underlying disorders. Another example are emerging studies that aim to assess the distinctiveness of features in light of symptom comorbidity [e.g., 111].

Characterizing progressive communication breakdown or network interactions as well as inter-individual variation in the brain's functional architecture requires large sample sizes. While R-FMRI is straightforward to collect, sample sizes needed for discovery science or hypothesis generation [15] lay beyond the data-collection capacity of single labs, especially for clinical populations. Fortunately, recent efforts highlighted the potential of aggregating R-FMRI datasets from multiple labs (e.g., ADHD-200: http://fcon_1000.projects.nitrc.org/indi/adhd200/; Autism Brain Imaging Data Exchange—ABIDE: http://fcon_1000.projects.nitrc.org/indi/abide/). Indeed, as R-FMRI does not involve complex or varying task designs, data aggregation is easier for R-FMRI than for task-based FMRI datasets. Importantly, even in light of between-lab variability, robust effects were observed [15, 111, 148]. Such successful data aggregation could be used to motivate inclusion of short R-FMRI scans in the diagnostic process of childhood psychiatric disorders. However, in light of limited replication of findings and limited diagnosis prediction accuracies (e.g., outcomes of the ADHD-200 competition), these R-FMRI scans would not serve diagnostic purposes yet. Nevertheless, their widespread inclusion would allow gathering large-scale datasets needed to index and ultimately overcome phenotypic heterogeneity. For instance, one way would be to side-step diagnosis completely and instead rank participants on a severity continuum using a combination of brain and behavioral data. By increasing our understanding of clinically and neurobiologically relevant subtypes, we ultimately create possibilities to improve the diagnostic process and develop treatment protocols tailored to an individual's specific (brain-related) characteristics. To reach this goal, we anticipate a shift in our scientific model from assessing individuals on a single occasion to monitoring subsequent stages of disorder development.

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Conflict of interest The authors declare that they have no conflicts of interest.

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