Review

Biological Psychiatry: CNNI

Intrinsic Functional Connectivity in Attention-Deficit/Hyperactivity Disorder: A Science in Development

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ABSTRACT

Functional magnetic resonance imaging without an explicit task (i.e., resting-state functional magnetic resonance imaging) of individuals with attention-deficit/hyperactivity disorder (ADHD) is growing rapidly. Early studies were unaware of the vulnerability of this method to even minor degrees of head motion, a major concern in the field. Recent efforts are implementing various strategies to address this source of artifact along with a growing set of analytic tools. Availability of the ADHD-200 Consortium data set, a large-scale multisite repository, is facilitating increasingly sophisticated approaches. In parallel, investigators are beginning to explicitly test the replicability of published findings. In this review, we sketch out broad, overarching hypotheses that are being entertained, while noting methodological uncertainties. Current hypotheses implicate the interplay of default, cognitive control (frontoparietal), and attention (dorsal, ventral, salience) networks in ADHD; functional connectivities of reward-related and amygdala-related circuits are also supported as substrates for dimensional aspects of ADHD. Before these can be further specified and definitively tested, we assert the field must take on the challenge of mapping the "topography" of the analytic space (i.e., determining the sensitivities of results to variations in acquisition, analysis, demographic and phenotypic parameters). Doing so with openly available data sets will provide the needed foundation for delineating typical and atypical developmental trajectories of brain structure and function in neurodevelopmental disorders, including ADHD, when applied to large-scale multisite prospective longitudinal studies, such as the forthcoming Adolescent Brain Cognitive Development study.

Keywords: ADHD, Default mode network, Functional connectivity, Literature, Resting-state, Review

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Examination of functional connectivity (FC) (1) during functional magnetic resonance imaging (fMRI) scans without an explicit task, other than remaining still (i.e., resting-state fMRI), began in 1995 (2). This initial observation did not gain momentum until the default mode network (DMN) of the brain was identified (3) and independently replicated using resting-state fMRI (4). Ever since, the number of resting-state fMRI studies has doubled every 2 years as the approach is applied across neuropsychiatry (5), including attention-deficit/hyperactivity disorder (ADHD). For example, a review by Posner *et al.* (6) published in 2014 covered 21 ADHD resting-state fMRI studies, whereas we include 76 reports (Supplemental Table 1). Neuroimagers have rapidly adopted resting-state fMRI methods because they can be applied across nearly the entire age range (7) and across ability levels (8), efficiently reveal whole-brain between-group differences (9), and can be used translationally across animal and human studies (10–12).

Besides numerical growth, quality of resting-state fMRI ADHD studies has also improved. Specifically, in the earlier review by Posner *et al.* (6), mean sample size was ~23 per group. Excluding analyses of the ADHD-200 Sample (13), mean sample size has grown to ~43 per group. Other factors remaining equal, larger samples increase statistical power (14).

Head motion is the most serious threat to resting-state fMRI ADHD study integrity (15–20). This concern was not even on the horizon when ADHD resting-state fMRI studies first emerged. Motion is always a concern in neuroimaging, but fMRI standards are inadequate for resting-state fMRI, which lacks a known task temporal structure. Head motion occurs at similar low frequencies as intrinsic blood oxygen level–dependent (BOLD) signal fluctuations and produces regionally distinct artifacts, which cannot be overcome by increasing sample size or scan duration (21). This motion is especially troublesome for ADHD, which is characterized by hyperactivity, even in adults (22). Results from studies that did not account for head micromovement artifacts must be considered tentative, as they are more likely than most studies to include false-positive findings (14,23). The complexity of this issue is highlighted by observations that in-scanner head motion correlates with impulsivity ratings (24). Global signal regression (GSR) during preprocessing mitigates between-subject effects of head motion (20), although GSR is controversial for potentially biasing group differences by

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enhancing negative correlations (25). An imperfect alternative is to "scrub" data (delete data points exceeding a threshold) (21), at least for confirmatory analyses. Compensatory methods are under active investigation (13,15–21,26–29), while efforts continue to address head motion during data acquisition (30) and analysis (31).

A counterweight to such concerns has been provided by the field's embracing a culture of open science (32) and open data sets (8). The ADHD-200 Consortium released 776 resting-state fMRI and structural scans with phenotypic data on March 1, 2011. Data aggregated from eight sites included 491 data sets from typically developing children and adolescents (TDC) and 285 from children and adolescents with ADHD (33). To recruit scientists from outside the ADHD field, the ADHD-200 Consortium announced a competition to discern the diagnoses (TDC, ADHD combined type, or ADHD inattentive type) of 197 unlabeled data sets, released on July 1, 2011, as raw or preprocessed data (33). There were 21 teams, and 12 articles documented their efforts (13,34–44). The best diagnostic results leveraged demographic biases inherent to ADHD (sex, handedness, IQ) without including neuroimaging (35). Still, multiple teams assigned diagnoses substantially above chance from neuroimaging parameters alone (45). This proof-of-principle effort was not intended to establish a novel diagnostic approach and did not do so. Instead, the challenge provided an initial milestone of progress. The ADHD-200 initiative has also supported numerous novel applications of analytic algorithms (46–57). As summarized elsewhere (45), neuroimaging is far from attaining psychiatric clinical utility, but initial progress is being made.

In this narrative review, we provide a snapshot of this rapidly developing field in anticipation of game-changing initiatives, such as the prospective large-scale longitudinal Adolescent Brain Cognitive Development (ABCD) study. We include peer-reviewed studies resulting from PubMed and Google Scholar searches of the conjunction of "ADHD" and "resting-state fMRI" and their synonyms as of December 30, 2015, and exclude studies lacking healthy comparisons. Our aim is to highlight lessons learned as the field invents itself, with an eye to the emergence of analytic and conceptual frameworks to be brought to bear on prospective longitudinal studies such as the ABCD study. These frameworks remain the gold standard for delineating typical and atypical developmental trajectories of brain structure and function (58). The heterogeneity of the literature summarized in Supplemental Table 1 precludes detailed descriptions. Instead, this review is organized around three themes: 1) principal measures and approaches employed, 2) studies bearing on the DMN interference hypothesis (59), and 3) emerging models/hypotheses of brain functional organization in ADHD that are accruing empirical support.

PRINCIPAL MEASURES AND APPROACHES

Although data collection is superficially simpler for resting-state fMRI than for task-based fMRI, the absence of an explicit task and its temporal structure allows nearly innumerable analytic approaches, which represents its own challenge. Six categories of analytic methods—seed-based correlations (SBC); independent component analysis (ICA); clustering; pattern classification; graph theory; and two local methods, regional homogeneity (ReHo) and amplitude of low-frequency fluctuations (ALFF)—have been extensively reviewed elsewhere (60). We briefly note measures used in ADHD resting-state fMRI studies to date.

Intrinsic FC Networks

The main challenge of SBC (i.e., examining correlations of time series between a region of interest ("seed") and remaining gray matter voxels) is constraining seed selection, as even minor variations matter (61). A popular alternative is ICA, which decomposes four-dimensional imaging data into three-dimensional spatial maps, each with its associated time course (62–64). As demonstrated by Yeo *et al.* (65), ICA components are remarkably replicable across groups. These maps of coherent spontaneous BOLD signal correspond to functional networks revealed by meta-analyses of task-based fMRI (9). Such networks can be defined by SBC (61,66–68) or ICA (9,65). Maps of cortex divided into seven ICA networks (65) based on resting-state fMRI scans of 1000 healthy young adults (available at https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation_Yeo2011) are increasingly being used as a strategy to reduce analytic dimensionality, as illustrated in the section on emerging models.

Voxelwise Indices of Intrinsic BOLD Signals

Theoretically, functional connectomics can encompass ($n * [n - 1]$)/2 distinct correlations (n = number of nodes, ≤ total number of voxels), incurring an immense multiple comparisons problem (69,70). An alternative is to survey voxelwise indices to identify regional between-group differences using statistical methods comparable to task-based fMRI. Among the earliest to be applied to ADHD was ReHo (71,72), an index of contiguous FC. Similar to all resting-state fMRI metrics, ReHo is affected by preprocessing (73), complicating across-study comparisons, which have conflicted (37,43,72,74–81). For example, in lingual gyrus, both increased ReHo (37,75,78) and decreased ReHo (72,81) were found. Still, in medial prefrontal cortex (PFC), reports converged on decreased ReHo in ADHD (37,75,78).

The ALFF, the total power within a low-frequency range, was first defined in a study on ADHD (82), although conflicting results have also been reported (83). A more methodologically rigorous effort (larger samples, medication-naïve patients) found decreased ALFF in ventral PFC and orbitofrontal cortex (OFC), along with increased ALFF in pallidum and dorsal PFC (84). In a head-to-head comparison of ALFF and ReHo, ReHo was more sensitive in detecting lower values in frontal-cingulate-occipital-cerebellar areas in ADHD (77).

An intriguing feature of intrinsic FC is the robust nature of homotopic (mirror image) FC relative to all other edges in the brain (85). These were highlighted in contrasts of FC among 90 anatomically defined nodes in samples comprising 239 children with ADHD from the ADHD-200 initiative, 39 adults with major depressive disorder, 69 adults with schizophrenia, and control subjects (86). Across all three diagnostic comparisons, partial correlations revealed that homotopic counterparts contributed 60%–76% of the altered Pearson values in FC abnormalities, suggesting that psychopathology in general entails altered interhemispheric communication (86).