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

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Abstract

Functional magnetic resonance imaging (fMRI) without an explicit task, i.e., resting state fMRI, 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 analytical tools. Availability of the ADHD-200 Consortium dataset, a large-scale multi-site repository, is facilitating increasingly sophisticated approaches. In parallel, investigators are beginning to explicitly test the replicability of published findings. In this narrative review, we sketch out broad, overarching hypotheses 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 analytical space, i.e., determining the sensitivities of results to variations in acquisition, analysis, demographic and phenotypic parameters. Doing so with openly available datasets 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 multi-site prospective longitudinal studies such as the forthcoming Adolescent Brain Cognitive Development study.

Keywords

ADHD; resting-state; default mode network; review; literature; functional connectivity

Examining functional connectivity (FC) (1) during fMRI scans without an explicit task, other than remaining still, i.e., "resting state" fMRI (R-fMRI), began in 1995 (2). This initial

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observation did not gain momentum until the brain's default mode network (DMN) was identified (3) and independently replicated using R-fMRI (4). Ever since, the number of R-fMRI studies has doubled every two years as the approach is applied across neuropsychiatry (5), including Attention-Deficit/Hyperactivity Disorder (ADHD). For example, a 2014 review by Posner et al. covered 21 ADHD R-fMRI studies (6), whereas we include 76 reports (See Table 1). Neuroimagers have rapidly adopted R-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, R-fMRI ADHD study quality has also improved. Specifically, in that earlier review (6), mean sample size was ˜23/group. Excluding analyses of the ADHD-200 sample (13), mean sample size has grown since to ˜43/group. Larger samples increase statistical power (14), other factors remaining equal.

Head motion is the most pernicious threat to R-fMRI ADHD study integrity (15-20). This concern was not even on the horizon when ADHD R-fMRI studies first emerged. Motion is always a concern in neuroimaging, but fMRI standards are inadequate for R-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 is especially troublesome for ADHD, which is characterized by hyperactivity, even in adults (22). Accordingly, results from studies which did not account for head micromovement artifacts must be considered tentative – as they are even more likely than most to include false positives (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 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 datasets (8). The ADHD-200 Consortium released 776 R-fMRI and structural scans with phenotypic data on March 1, 2011. Data aggregated from eight sites included 491 datasets 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 Consortium announced a competition to discern the diagnoses (TDC, ADHD combined type, or ADHD inattentive type) of 197 unlabeled datasets, released on July 1, 2011 as raw or pre-processed data (33). Twenty-one teams competed and 12 papers documented their efforts (13;34-44). Ironically, 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, nor did it. Instead, the challenge provided an initial

milestone of progress. Importantly, 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 studies resulting from PubMed 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 analytical and conceptual frameworks to be brought to bear on prospective longitudinal studies such as ABCD. These remain the gold standard for delineating typical and atypical developmental trajectories of brain structure and function (58).

The heterogeneity of the literature summarized in 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 R-fMRI than for task-based fMRI, the absence of an explicit task and its temporal structure allows nearly innumerable analytical 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). Here we briefly note measures used in ADHD R-fMRI studies to date.

Intrinsic Functional Connectivity 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, since even minor variations matter (61). A popular alternative is ICA, which decomposes 4D imaging data into 3D spatial maps, each with its associated time course (62-64). As compellingly demonstrated by Yeo, Krienen et al. (65), ICA components are remarkably replicable across groups. These maps of coherent spontaneous BOLD signal correspond strikingly to functional networks revealed by meta-analyses of task-based fMRI (9). Such networks can be defined by SBC (e.g., 61;66;67;68) or ICA (9;65). Maps of cortex divided into seven ICA networks (65) based on R-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.

Voxel-wise 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 voxel-wise indices to identify regional between-group differences using statistical methods comparable to task-based fMRI. Among the earliest to be applied to ADHD was regional homogeneity (ReHo) (71;72), an index of contiguous FC. Like all R-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).

Amplitude of low-frequency fluctuations (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 fronto-cingulo-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 brain (85). These were highlighted in contrasts of FC among 90 anatomically-defined nodes in samples containing 239 children with ADHD from the ADHD-200 initiative, 39 adults with major depression, 69 adults with schizophrenia, and their respective controls (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).

Entropy measures, derived from information theory, index repeatability or randomness (87). Sample entropy of BOLD time series was reduced in anterior cingulate cortex (ACC), superior frontal gyrus, precuneus and cuneus in a small sample of adults with ADHD, indicating lower complexity (88). By contrast, entropy applied to network clusters (termed graph spectral entropy) was increased in ADHD in pre- and postcentral gyrus, superior temporal gyrus, and inferior frontal gyrus (IFG) in ADHD-200 data (89). This was interpreted as indicating abnormal network structure in ADHD, our focus in the next section.

Graph Theory

The complexity of the functional connectome (90) also invites graph theoretical approaches in which regions-of-interest are abstracted as network nodes and their relationships, including correlations, as edges (91). This allows application of a family of indices including path-lengths, their efficiencies (relative to random or lattice-like networks), and measures of centrality or hubness (91). Decreased global efficiency has been found in adults (92) and children with ADHD (93). Mapping the density of local FC (all correlated contiguous voxels exceeding a given threshold – this differs from ReHo, which examines the average

correlation among contiguous voxels) revealed 15% higher local FC in OFC, ventral striatum, and superior frontal cortex, regions associated with reward and motivation, whereas long-distance FC density (the difference between local FC and whole-brain FC) was 33% lower in superior parietal cortex and posterior DMN (55).

Centrality measures have been used to contrast children with ADHD and TDC to children with autism spectrum disorder (94). Shared abnormalities were found in the patient groups in precuneus, whereas increased degree centrality in striatum and pallidum was associated with ADHD, with or without comorbid autism (94). The two neurodevelopmental disorders and TDC were also contrasted on the topographic structure of the connectome (95). In this pilot study, children with autism (n=16) differed from those with ADHD and from TDC in exhibiting higher structural and functional connectivity, but only inside “rich-club” networks, i.e., those composed of highly connected hubs (95).

The hierarchical nature of brain information transfer (96) supports the use of “step-wise FC” to discretize FC into distinct relay steps from primary cortex to executive processing and DMN areas (97). Children with ADHD, selected from group-matched ADHD-200 subsamples (n=120/group), showed greater FC within primary cortex and decreased step-wise FC to attention-regulatory networks; increased step-wise FC to DMN also characterized ADHD (98).

Test-retest Reliability

A marker of scientific maturity is the extent to which methods have been standardized, particularly whether measurement reliability has been quantified. In this regard, R-fMRI has a ways to go (but see the Consortium on Reliability and Replicability dataset for a novel resource (99)). In ADHD, one study examined short-term (intra-session) test-retest reliability of four R-fMRI indices (ALFF and fractional ALFF, ReHo, and FC of posterior cingulate cortex (PCC), a core DMN node) (100). These short-term best-case reliability estimates yielded moderate-to-high values. Still, for most indices, controls were significantly more reliable than patients in some brain regions (100). These preliminary findings highlight the importance of examining longer-term (i.e., one week) test-retest reliability across ages (beyond the one small study documenting test-retest reliability in children (101)), by sex, and in each clinical condition-of-interest as part of the foundational work required to build a scientific edifice. Since the maximum obtainable validity cannot exceed the square root of reliability, reliabilities should be factored into realistic power estimations.

Default Mode Network Interference Hypothesis

In ADHD, the coincidence of low frequency fluctuations in response time variability (RTV) (102-104) with the low frequency interplay between DMN and networks involved in top-down executive control (66;105;106) motivated formulation of the DMN interference hypothesis (59). This was initially examined indirectly in a pair of reports based on a pilot sample of adults with ADHD and controls (n=20/group) (107;108). Of three seeds previously associated with momentary lapses of attention in healthy adults (109), SBC of a spherical right dorsal ACC seed revealed a between-group difference in FC with PCC/precuneus, i.e., decreased negative correlation magnitude in ADHD (107). Secondary

analysis using PCC/precuneus as a seed revealed significant attenuation in positive correlation strength between anterior (ventromedial PFC) and posterior DMN components (107).

Sun et al. sought to replicate and extend Castellanos et al. (107) in a study of 19 medication-naïve boys with ADHD and 23 healthy controls (110). Using an anatomically-defined dorsal ACC seed and GSR, they found loss of the normative negative relationship between dorsal ACC and retrosplenial gyrus, lingual gyrus, dorsomedial PFC and PCC in ADHD (110).

In another explicit test of replicability, controls and individuals with persistent or remitting ADHD were contrasted 16 years after initial evaluation (111). Mattfeld et al. explicitly tested the finding of lower FC between DMN posterior and anterior nodes in adults with ADHD, using the same PCC seed as (107). They obtained the same result, even without GSR, but only in the 13 young adults with persistent ADHD (111). They also examined medial PFC, using a previously published seed, and observed negative FC with dorsolateral PFC in controls which was absent in both ADHD remitters and persisters (111).

The relationship between DMN and the Yeo-Krienen networks (65) – including the ventral attention network (112) – was examined ingeniously in ADHD-200 data by Sripada and colleagues. They selected subsets of 133 patients with ADHD and 288 controls for three studies (51;54;113). In the first (54), they computed FC among 907 seeds throughout cortex grouped per the seven Yeo-Krienen networks (65). They found lower within-DMN FC and between DMN and ventral attention, frontoparietal and visual networks. Functional connectivity between ventral attention and frontoparietal networks was also reduced in ADHD (54). They further identified lower FC between key ventral attention nodes and DMN which replicated the Castellanos et al. result (107), extended to anterior insula. Finally, abnormal internetwork FC with DMN was predominantly right lateralized, consistent with anatomic findings (114).

In another innovative contribution by the same group, joint ICA was used to test the hypothesis that structural deficits parallel altered FC (51). They found four components which linked lower magnitude anti-correlation between DMN and cognitive control networks co-occurring with structural abnormalities in dorsolateral PFC and dorsal ACC. They also observed altered intra-network FC in DMN, dorsal attention, and visual networks, again co-occurring with structural deficits (51). Their approach represents a model for integrating analyses across multimodal imaging data types, rather than continuing to examine them in isolation.

One study has focused on the DMN cerebellar component in adults with ADHD, finding increased FC to multiple cortical networks, including visual, dorsal attention, salience and sensorimotor (115). This effort was overdue, given extensive volumetric evidence of cerebellar involvement in ADHD (116).

In summary, although far from unanimous (e.g., 117;118;119;120), weaker within-DMN FC has been observed in adults (107;108;111) and in children (51;54;110;121;122) with ADHD. Decreased magnitude of negative FC between DMN and dorsal ACC has also been repeatedly noted (51;54;107;110), but see (123). However, this rudimentary relationship may

be part of more complex inter-network relationships, as we suggest below, after first discussing dimensionality and putative age-relationships.

Emerging Models of Brain Functional Organization in ADHD

Dimensional Brain-Behavior Relationships

Barber et al. conducted the first R-fMRI study including RTV indices in children with ADHD (117). They performed SBC with seeds in DMN and cingulo-opercular network (124) (which overlaps with the ventral attention network (65) and the salience network (125)). They found increased FC within both networks in ADHD; for the cingulo-opercular network, this was localized to supplementary motor area; FC was also increased between DMN seeds and inferior OFC and temporal pole (117). In both groups, greater negative FC between DMN and occipital regions was associated with reduced variability on RTV indices, whereas greater negative FC between DMN and lateral PFC areas was related to fewer errors (117). This well-designed study (n=50/group) provides a template for incorporating both categorical (diagnostic) and dimensional perspectives.

In other examples of dimensional approaches, slower stop task inhibition was related to thalamus-ACC FC (126), impulsive responding on temporal discounting was associated with increased FC between nucleus accumbens and PFC (127), and spatial working memory performance was linked to thalamicputamen and thalamic-PFC FC (52), regardless of presence or absence of ADHD diagnosis. However, some relationships differ depending on diagnosis. Examples of both shared and distinct dimensional relationships between parent ratings and FC indices for children with ADHD and TDC were first illustrated in a moderately sized sample (37/group) (128) and extended beyond DMN in 300 children from the ADHD-200 initiative (50). A particularly innovative study combined symptoms, temperament scales, and electrocardiographic physiology measures to differentiate 247 children with ADHD into “mild,” “surgent” and “irritable” phenotypes (129). R-fMRI data were only available for 39 children with ADHD (18 mild, 11 surgent and 10 irritable) and 15 controls, but they still revealed intriguing differences in amygdala FC among the ADHD phenotypes as well as between controls and ADHD subgroups. Remarkably, in longitudinal follow-up, the data-driven irritable subtype developed a new comorbid disorder at twice the rate of the other subgroups (129).

Affective/limbic circuitry is increasingly being examined in ADHD (129-133). For example, amygdala SBC has been used to validate phenotyping (129), to dissociate emotional regulation and executive attention (130), in relation to aggressiveness and conduct problems (132), as a correlate of emotional lability (131), and of depressive symptoms (133). Similarly, striatum, long implicated in ADHD, has been targeted frequently (120;126;127;130;134-136).

Age-related Differences Consistent with Maturational Delay

Delay in cortical maturation was convincingly reported in the landmark NIMH longitudinal study of ADHD (137). Age-related abnormalities were found in meta-analysis of cross-sectional studies of N-acetylaspartate in medial PFC (138). R-fMRI studies have also

yielded cross-sectional results interpreted as consistent with maturational lags in ADHD (56;98;113;121;122).

The most suggestive results have been obtained using ADHD-200 data because of its substantial size, despite the limitations of cross-sectional data for inferring developmental trajectories (58). For example, using the same ADHD-200 subsets (51;54), Sripada et al. used whole-brain connectomics methods (69) to focus on age-related differences in inter-network FC (113). They found cross-sectional results consistent with maturational lag of FC within DMN and between DMN and frontoparietal and ventral attention networks (113). These results are compatible with longitudinal structural findings (137) and will likely become primary hypotheses-of-interest for the ABCD Study.

Tomasi and Volkow used ADHD-200 data (203 children with ADHD and 402 TDC), along with 704 healthy adults from the 1000 Functional Connectomes Project (139) to examine ventral tegmental area (VTA) and substantia nigra SBC (56). They found evidence of age-related differences between children and adults: higher VTA FC in children with ADHD with thalamus and pallidum, and higher substantia nigra FC with amygdala and insula (56). Once again, these represent key hypotheses for longitudinal confirmation.

Finally, age-related factors were examined in a longitudinal follow-up of 129 adolescents with ADHD in childhood and 100 controls scanned at about age 17.5 years (120), with FC examined in relation to baseline and follow-up ADHD scores and their changes. Findings support the hypothesis that ADHD remission results from prefrontal maturation (140). Specifically, improvement in hyperactive/impulsive score was related to stronger correlation between ACC and executive control network as defined by (9). Lin et al. also focused on the bilateral frontoparietal network, finding decreased FC between anterior PFC and ventrolateral PFC in children with ADHD that was robust to three different preprocessing strategies (141).

Multi-network Models in ADHD

Despite the attractiveness of simple models consisting of dorsal ACC-DMN FC or within-DMN FC, more complex alternatives have begun to be proffered. Menon proposed a triple network model (125) comprising frontoparietal central executive network (CEN), DMN, and salience network (142). Menon hypothesized that many psychiatric conditions, including ADHD, are characterized by inappropriate engagement of the salience network with CEN and DMN (125). A novel measure, the resource allocation index (RAI), represents cross-network interactions (122). Quantitatively, RAI equals the difference in FC values between two sets of FC relationships: salience network and CEN, and salience network and DMN (47). The first application of the RAI was conducted by Choi and colleagues (122). This small study (n=20/group) found interactions between diagnostic group and age. Medication-naïve children with ADHD did not show the increase in RAI with increasing age found in TDC (122). The same RAI was applied to ADHD-200 samples from three sites (47). Across all three sites, RAI was lower in ADHD, indicating a stronger correlation between salience network and DMN than between salience network and CEN in ADHD (47). By contrast, single network analyses or two-network interactions did not exhibit the same consistency (47). Determining RAI “transportability” across samples (i.e., replicability and sensitivity to

demographic, acquisition and analytical factors) should be a priority, as it could unify heretofore fragmented perspectives on ADHD and psychopathology more broadly (125).

A multi-network SBC examination in adults with ADHD differentiated four: salience, DMN, dorsal and ventral attention (143). The authors found decreased salience to dorsal attention network FC in ADHD, whereas dorsal and ventral inter-network FC was increased (143). Patients with ADHD also exhibited greater within-network FC in DMN and ventral attention network (143).

These reports (47;122;143) illustrate the obstacles posed by variations in nomenclature and network boundaries. Encouragement by reviewers and editors to use common frameworks, such as the Yeo-Krienen networks (65), at least for supplementary analyses, would hasten resolution of such ambiguities.

An impressive example of data-driven models of attention-related networks was provided by Rosenberg et al. (144). First, healthy young adults performed task-based fMRI with a novel continuous performance test. Their index of sustained attention, d', was used to discern the most positively and negatively associated f-MRI edges in a connectome matrix of 268 nodes (144). The resulting high-attention and low-attention networks robustly predicted d' values from the same individuals' R-fMRI data (144). Remarkably, the high-attention and low-attention networks defined in adults from fMRI task performance also predicted ADHD scores for children from a single ADHD-200 site. Finally, FC models defined on data from the ADHD-200 subjects predicted d' in the original healthy adults. By contrast to the reduced models on which we have focused heretofore, this robust and apparently generalizable model comprises "wide swaths of cortex as well as subcortical regions and the cerebellum" (144). Once again, the extent to which these networks and approaches can generalize even more broadly will reveal whether the work of building a scientific edifice using R-fMRI has begun to "touch bedrock."

Conclusions

ADHD R-fMRI investigators continue to innovate methodologically (e.g., 136;145;146;147) while increasingly addressing the nefarious effects of head micromovements (29;30). Although it is not yet possible to distill the mosaic of heterogeneous reports into a single conclusive story, several overarching hypotheses are emerging that are amenable to being tested in large-scale, longitudinal, prospective cooperative efforts, such as the forthcoming ABCD study. In ADHD, at a minimum these include decreased synchrony between the anterior and posterior nodes of the DMN (51;54;107;108;110;111;121;122); the interplay of DMN (including cerebellum), frontoparietal (i.e., executive control), and attention (ventral, dorsal and salience, depending on nomenclature) networks (51;54;107;110); the involvement of reward-related circuits (including OFC, ventral prefrontal, and ventral striatum) in hyperactivity/impulsivity (56;120;126;127;130;134-136); the role of amygdala FC in emotional regulation (129-133); and delays/alterations in maturational trajectories of all of these candidate systems (56;98;113;121;122). Voxel-wise measures have been more divergent, although decreased ReHo in medial PFC has been reported repeatedly (37;75;78).

Still, the analytical search space remains vast, with innumerable options, each producing divergent results. Fortunately, the availability of open datasets is facilitating efforts to perform head-to-head comparisons of analytical strategies (148;149). Explicit replication of published results (e.g., 107) remains the exception (54;111); across-site comparisons have ranged from encouraging (47) to cautionary (49). As funding agencies increasingly require fast and open access to large-scale research data and emphasize reproducibility (150), the field has the opportunity to extend the metaphor of brain mapping into *analytical topography*. This entails quantifying reliability, and charting the "contours" of the analytic space to determine the sensitivities of brain-behavior relationships and group-differences to the myriad features (acquisition parameters, analytic strategies, demographic and phenotypic factors) that influence them. This is already occurring as reviewers and editors (ourselves) invite, encourage, and eventually require supplementary analyses with alternative preprocessing and conceptual frameworks. In so doing, we can hasten the advance toward a true science of brain function with clinical utility.

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		ADHD			Controls					Motion Inclusion Criteria	Preprocessing								
* Author	Year	N	Age	SD	N	Age	SD	Scan Duration	Eyes		Nuisance Covariates	Software, pipeline, if specified	Scrubbing? Threshold	GSR	Regions-of-interest	Method or index	Results Related to Intrinsic Brain Activity	GS Cites	Comments
Cao,Q. (72)	2006	23	13.4	1.5	21	13.3	1.0	8min	Closed	2mm or 1°	N/A	SPM2, AFNI	No	No	WBA	ReHo	ReHo ↓ in frontal striatal cerebellar circuits, ↑ in occipital cortex in ADHD	189	Earliest use of ReHo, local connectivity index, in ADHD
Tian (123)	2006	8	13.9	0.4	8	13.4	0.5	8min	Closed	1mm in 150 continuous volumes	N/A	SPM2, AFNI	No	No	dACC	SBC	↑ FC between dACC and thalamus, cerebellum, insula, brainstem (all bilateral) in ADHD	283	dACC seed size/definition unclear; extremely small samples
Zang (82)	2007	13	13.0	1.4	12	13.1	0.6	8min	Closed	4SD	N/A	SPM2, AFNI	No	No	WBA	ALFF	ALFF ↓ in the R IFG, L sensorimotor cortex, and bilateral cerebellum and vermis; ↑ in R ACC, L sensorimotor cortex, and bilateral brainstem	749	First use of amplitude index ALFF in ADHD; small samples
Castellanos (107)	2008	20	34.9	9.9	20	31.2	9.0	6.5min	Open	N/A	6 MP, CSF, WM, global signals	AFNI, FSL	No	Yes	dACC, R IFG, R MFG	SBC	↓ negative FC between dACC and precuneus/PCC	532	Pilot study; highlighted FC between dACC and precuneus/PCC
Tian (147)	2008	8	13.5	1.1	10	13.2	0.6	8min	Closed	1mm in 150 continuous volumes	N/A	SPM2, AFNI	No	No	WBA	Resting state activity index (RSAI)	RSAI ↑ in bilateral visual cortex (BA 17/18/19), L sensory cortex (BA 3), L auditory cortex (BA 22), bilateral thalamus, L dorsal brainstem, and midbrain in ADHD	94	Same sample as Tian 2006 (112); RSAI is a unique measure = ReHo times the SD of ALFF. Not used since in ADHD
Uddin (108)	2008	20	34.9	9.9	20	31.2	9.0	6min 34s	Open	N/A	6 MP, CSF, WM, global signals (confirmed w/ senior author)	AFNI, FSL	No	No	DMN	Network homogeneity	↓ network homogeneity in DMN	242	Same sample as Castellanos 2008 (97); introduced novel index of network homogeneity. Not used since in ADHD
Zhu (74)	2008	9	N/A	N/A	11	N/A	N/A	8min	N/A	1.2mm or 1.2°	N/A	SPM2, AFNI	No	No	WBA	ReHo	ReHo in PFC and ACC discriminated ADHD; Fisher discriminative analysis (85% accurate) outperformed SVM (75%) and Batch Perceptron (55%) machine learning methods.	146	First instance of machine learning methods in ADHD. Extremely small sample.
Cao,X. (134)	2009	19	13.3	1.4	23	13.2	1.0	8min	Closed	3mm or 3°	6 MP, CSF, WM, global signals	SPM5, REST	No	Yes	Putamen	SBC	↓ putamen FC with subcallosal gyrus, SFG, precuneus, STG, & declive; putamen FC ↑ in R globus pallidus/ thalamus in ADHD	109	Medication naïve subset of subjects from Cao,Q. 2006 (64)
Wang (93)	2009	19	13.6	1.5	20	13.3	1.0	8min	Closed	2mm or 1.5°	6 MP, global signal	SPM5, AFNI	No	Yes	90 AAL regions	Small world properties	↓ global efficiency in ADHD; ↓ nodal efficiency in OFC, rectus gyrus, lingual gyrus, MTG, ITG, temporal pole; ↑ local efficiency in IFG, triangularis, and pallidum in ADHD	241	First graph theory study in ADHD
Fair (121)	2010	23	10.6	2.9	23	10.0	2.6	2 * 5min or 3 * 3.5min	Open	2mm	6 MP, CSF, WM, global signals	In-house pipeline	No	Yes	DMN seeds	SBC	↓ integration of DMN; results interpreted as consistent with disruption of maturational processes	167	12 DMN seeds derived from previous study in adults; results interpreted as consistent with delayed maturation, although based on cross-sectional data
Liu (75)	2010	23	N/A	N/A	23	N/A	N/A	8min	Closed	N/A (2 excluded)	N/A	SPM5, REST	N/A	N/A	WBA	ReHo based on coherence (Cohe-ReHo) compared to ReHo based on Kendall's coefficient of concordance (KCC-ReHo)	CoHe-ReHo was more sensitive than KCC-ReHo to between-group differences in diagnosis	47	Introduced novel approach to measure ReHo based on spectral coherence; the novel measure was more sensitive, but has not been used again in ADHD
Qiu (146)	2011	15	12.7	1.8	15	13.2	1.7	5min 20s	Closed	N/A	N/A	SPM5, FSL MELODIC	No	No	DMN	Multi-modal (T1 structural, DTI, resting state fMRI)	DMN FC ↓ in ACC, PCC, lateral PFC, L precuneus and thalamus, ↑ in bilateral posterior medial PFC in ADHD	84	All results uncorrected for multiple comparisons; small samples
Yang (83)	2011	17	10.0	2.0	17	9.7	1.6	6min 40s	Closed	3mm or 3°	N/A	AFNI	No	No	WBA	ALFF	ALFF ↑ in L SFG, sensorimotor cortex, ↓ in bilateral ACC, middle cingulate and R MFG	36	Medication-naïve patients; brief report of use of short TR (400ms) to improve temporal resolution
Bohland (34)	2012	272	N/A	N/A	482	N/A	N/A	8 sites from ADHD-200	Both	No	6 MP, CSF, WM signals, low-order polynomials	FSL, AFNI, Athena	No	No	FreeSurfer structural indices; AAL parcellation yielded > 12,000 features	Machine learning	Predictability significantly greater than chance for both cross-validation analyses and held-out test data	18	Predictive features found diffusely throughout the brain
Brown (35)	2012	239	11.7	2.9	429	12.4	3.3	8 sites from ADHD-200	Both	108 participants excluded but criteria unspecified	6 MP	SPM8, in-house	No	No	Robust feature extraction	Machine learning	Best accuracy on hold-out dataset (62.5%) was obtained by predicting diagnosis using personal characteristic data, vs. 60.5% using fMRI data, both of which exceeded chance (55%)	26	Results highlighted challenges of real-world data
Chabernaud (128)	2012	37	9.7	1.6	37	10.2	2.0	6min	Both	N/A	6 MP, CSF, WM, global signals	AFNI, FSL	No	Yes	DMN seeds	SBC & dimensional/categorical phenotypes	Consistent dimensional relationships found between DMN FC and both internalizing and externalizing scores	38	First identication of hybrid (categorical and dimensional) models of brain-behavior relationships

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																	across groups; also some DMN FC relationships interacted with diagnoses		
Chang (36)	2012	210	11.8	2.8	226	12.4	3.0	6 sites from ADHD-200	Both	N/A	6 MP, CSF, WM, global signals	In-house software for structural index; Athena	No	No	SVM based on AAL, Craddock 200 parcellations	Texture-based feature extraction of structural MRI data: local binary patterns on three orthogonal planes vs. FC	Structural index provided better discriminative power (max accuracy = 0.70) than resting state data (max accuracy = 0.58)	14	Only male subjects retained. Best results found for whole brain texture distribution; no advantage from more focal parcellations
Cheng (37)	2012	98	12.1	2.0	141	11.4	1.9	1 site from ADHD-200	Both	3mm or 3°	6 MP, CSF, WM, global signals	AFNI, FSL	No	Yes	Craddock 400 parcellation	Brain-wise association study of multiple features including FC, fALFF, ReHo	In data from a single site, SVM classifier achieved cross-validated accuracy of 0.76, with most discriminative features associated with frontal and cerebellar regions	28	Cerebellar results unspecified
Cocchi (76)	2012	16	22.9	-	18	22.8	-	8min	N/A	2mm or 2°	6 MP, CSF, WM signals; multiple MP in analytical model	DPARSF	N/A	No	90 × 90 AAL connectivity matrix	Network analysis and ReHo	↑ nodal clustering coefficient in L OFC and R STG, ↓ path length in R MFC and superior occipital cortex in ADHD. Network-based analyses identified two multi-node cnetworks which also correlated with symptoms	58	Ingenious recruitment strategy: medication-naive previously undiagnosed individuals with ADHD recruited from an entire medical school class; intriguing identification of multi-node networks; replicability uncertain
Colby (38)	2012	285	N/A	N/A	491	N/A	N/A	7 sites from ADHD-200	Both	None	6 MP, CSF, WM, global signals	Athena	N/A	No	Harvard-Oxford, Craddock 400, and 90 functional units from Stanford FIND lab	Structural, functional and demographic data features selected and applied to test data from each site. Votes from multiple approaches used to assign class labels	Diagnosis of ADHD predicted with accuracy of 0.55 vs. 0.39 expected by chance	32	Sophisticated aproach to multi-site multi-modal data; sobering conclusions regarding modest effects
Dai (39)	2012	222	11.6	N/A	402	12.2	3.2	7 sites from ADHD-200	Both	2mm	N/A	REST, Athena	N/A	N/A	Craddock 400 parcellation	Recursive feature extraction and multi-kernel learning applied to ReHo, FC and structural indices	FC showed higher accuracy of predicting ADHD than ReHo. Integrating multi-modal features through multi-kernel learning produced highest accuracy	31	Thoughful exploration of challenges of multi-site data, with particular focus on imbalanced samples across sites
Dey (40)	2012	266	N/A	N/A	468	N/A	N/A	7 sites from ADHD-200	Both	N/A	6 MP, CSF, WM signals	Athena	N/A	N/A	7 ROIs identified by the authors	PCA-linear discriminant analysis applied to network features	Classification rates of 64% to 70% achieved with several network indices	11	Site-by-site results surprisingly consistent
Eloyan (41)	2012	274	N/A	N/A	491	N/A	N/A	8 sites from ADHD-200	Both	N/A	Motion, CSF, WM signals	1000 Functional Connectomes, Athena, DARTEL	N/A	No	Motor network	Feature extraction and machine learning on CUR-decomposition of FC data; FC in motor cortex	CUR decomposition feature extraction revealed motion artifacts which differed by diagnoses. Diagnostic accuracy 78% (specificity 84%, sensitivity 53%). Motor cortex analysis also revealed between-group and subtype differences, but not likely useful for individual-level results	44	Winning entry in ADHD-Competition
Mennes (126)	2012	17	11.0	1.3	17	10.8	1.9	6.5min	Open	4mm max displacement between consecutive timepoints	6 MP, CSF, WM, global signals	AFNI, FSL	0.5mm	Yes	11 fronto-striatal seeds from prior Stop task study	Relation between FC matrix index and Stop task indices measured after the scan	Slower inhibition associated with ↑ positive FC between R thalamus and ACC regardless of diagnosis; other relationships varied depending on diagnosis	16	Data lost from 46% of initial sample, possibly from fatigue, as Stop task performed after scan
Mills (52)	2012	94	8.7	0.8	132	8.5	0.7	5 sites from ADHD-200	Both	1.5mm RMS	6 MP, CSF, WM, global signals	N/A	3SD+ mean signal change	Yes	5 thalamic ROIs, thalamo-striatal FC	SBC	↑ thalamic and basal ganglia FC in ADHD confirmed in independently collected ADHD-200 data	45	ADHD-200 group data used to replicate original findings
Olivetti (42)	2012	351	N/A	N/A	572	N/A	N/A	8 sites from ADHD-200	Both	No	6 MP, CSF, WM signals	Athena, DARTEL	N/A	No	WBA	Structural, ReHo, and spatial multiple regression of 10 intrinsic networks examined for batch effects	Prediction accuracy strongly affected by batch effects: decreased from 80% to chance level when such correlated effects removed	5	Cautionary framework regarding complex designs and multi-site analyses
Sato (53)	2012	21	36.5	7.1	42	26.1	N/A	6.58min	Open	N/A	N/A	FSL	N/A	N/A	PCC, dACC	Spectral coherence analysis, one class-SVM	ADHD showed abnormal PCC/dACC coherence	16	Reanalysis of NYU data; includes subjects from Castellanos 2008 (97); Uddin 2008 (98)
Sato (43)	2012	383	11.6	3.0	546	12.3	3.5	8 sites from ADHD-200	Both	N/A	6 MP, CSF, WM signals	Athena	No	No	Craddock 400 parcellation	fALFF, ReHo, ICA defined DMN and task-positive network	Combining fALFF and ReHo modestly discriminated patients from controls; combining all three types of indices discriminated combined from inattentive type (67% accuracy). Regions conveying discriminative information distributed diffusely	26	Unexpectedly, DMN-task positive network did not contribute to discrimination of patients and controls
Sidhu (44)	2012	245	N/A	N/A	423	N/A	N/A	7 sites from ADHD-200	Both	108 excluded per ADHD-200 Preprocessed Initiative criteria	In-house; unspecified filtering used to remove noise	SPM8	No	No	WBA	FFT, kernel PCA over space and time, SVM	Adding imaging after dimensionality reduction improved diagnostic discrimination slightly more than when limited to phenotypes	21	Accuracy improved by ~2-3%; proof-of-principle in a challenging “real-world” application
Sun (110)	2012	19	13.3	1.4	23	13.2	1.0	8min	Closed	3mm or 3°	6 MP, CSF, WM, global signals	SPM5, REST	No	Yes	dACC defined per AAL	SBC in medication-naïve sample	↓ negative FC between dACC and anterior and posterior nodes of DMN in	60	First explicit replication and extension of Castellanos 2008 (97)

* Author	Year	ADHD N	ADHD Age	ADHD SD	Controls N	Controls Age	Controls SD	Scan Duration	Eyes	Motion Inclusion Criteria	Preprocessing Nuisance Covariates	Software, pipeline, if specified	Scrubbing? Threshold	GSR	Regions-of-interest	Method or index	Results Related to Intrinsic Brain Activity	GS Cites	Comments
																	ADHD; for R MTG, ADHD had negative dACC FC vs. null in controls		
Tomasi (55)	2012	247	11.2	N/A	304	11.2	N/A	4 sites from ADHD-200	Both	Mean FD < 0.3mm	6 MP, CSF, WM signals	SPM2	No	No	WBA	FC density mapping; long-range and short-range	↑ short-range FC density in reward/ motivation areas (OFC, ventral striatum, superior frontal) in ADHD; ↓ short-range FC density in posterior DMN; ↓ long-range FC density in cerebellum and superior parietal cortex	131	First paper published from ADHD-200 sample; leveraged a computationally efficient approach for contrasting whole-brain FC; consistent with dual-pathway (reward/motivation and cognitive-control) model of ADHD pathophysiology
An (77)	2013	19	13.3	1.4	23	13.2	1.0	8min	Closed	3mm or 3°	N/A	SPM5, REST	No	No	WBA	ReHo and ALFF	ReHo more sensitive than ALFF in detecting between-group differences in fronto-cingulo-occipital-cerebellar areas	18	Medication-naïve sample; data are part of the dataset analyzed by Cao, Q 2006 (64), Zang 2007 (74), Tian 2006 (112); secondary uncorrected analyses of ALFF with more smoothing yielded some convergence with ReHo results
An (78)	2013	23	12.5	1.8	32	11.8	1.8	8min	Closed	3mm or 3°	N/A	SPM8, REST	No	No	WBA	ReHo in double-blind placebo-controlled acute trial of methylphenidate	↓ ReHo in bilateral SFG; ↑ in sensorimotor, motor, visual cortex in ADHD; all acutely normalized by methylphenidate	20	First placebo-controlled double-blind comparison of methylphenidate in ADHD; seven children rescanned after 8-weeks treatment; preliminary evidence of potential utility for tracking treatment benefits
Choi (122)	2013	20	10.2	2.7	20	10.6	2.5	7min	Closed	N/A	Artifact removel by ICA	FSL, MELODIC	No	No	Salience (SN), DMN and Central Executive (CEN) Networks	ICA; Resource Allocation Index (RAI) = subtraction of SN-DMN FC from SN-CEN FC	ADHD did not show age-related increment of FC observed in controls	9	Discussion focuses on age-related differences, although study is cross-sectional; group differences in anterior-posterior DMN (as in Uddin 2008 (98)) reported but not highlighted; RAI based on Menon's 2011 tri-network model (114); age-related group differences did not survive correction for multiple comparisons
Costa Dias (127)	2013	35	9.6	1.5	64	9.21	1.2	3 *3.5 min	Open	1.5mm RMS	6 MP, CSF, WM, global signals	In-house pipeline	FD > 3SD + mean	Yes	WBA with nucleus accumbens seed	Relation between performance on delay discounting task and nucleus accumbens FC	Atypical FC between accumbens and PFC related to impulsivity in ADHD	51	Categorical (ADHD diagnosis +/−) and dimensional (delay discounting) analyses converged; comendable incorporation of RDoC approach
Di Martino (94)	2013	45	9.9	1.8	50	10.1	1.8	3 * 3.5min	Both	Mean FD < 0.3mm	6 MP, CSF, WM global signals	AFNI, FSL	0.2mm	Yes	WBA	Three group comparison of degree centrality (autism vs. ADHD vs. controls)	Centrality ↑ in precuneus in both autism and ADHD, ↑ in R striatum/pallidum related to ADHD symptoms	72	Among first papers to address comorbidity of autism and ADHD; both shared and distinct abnormalities observed
Fair (13)	2013	192	10.8	N/A	455	14.4	N/A	6 sites from ADHD-200	Both	1.5mm RMS	CSF, WM global signals	In-house pipeline	No	Yes	160 ROIs from Dosenbach 2010	160 × 160 correlation matrices	Atypical connectivity is prominent in DMN and insular cortex in ADHD-C, which in the DLPFC and cerebellum in ADHD-I.	122	Intended to be the "consortium paper" announcing ADHD-200 sample; was in revision when concerns regarding micromotion artifacts arose; 10 distinct strategies implemented to mitigate such artifacts; final analyses incorporated various strategies and motion-matched, low-motion subsets for all 3 groups
McCarthy (119)	2013	16	24.5	8.3	16	24.4	8.0	7.2min	N/A	3mm or 3°	CompCor for WM, CSF and motion components	SPM8, CONN	No	No	Affective network, ventral and dorsal attention, cognitive control network and DMN	SBC for 5 networks; adults with ADHD previously diagnosed in childhood	↓ FC in ventral and dorsal attention networks, ↑ FC in affective and DMN and R lateralized cognitive control network in ADHD	25	Small heterogeneous samples; results consistent with Tian 2006; contrary to Castellanos 2008, Fair 2010, Uddin 2008
Posner (130)	2013	22	10	1.6	20	10.5	1.4	2 * 5min	Closed	1.5mm RMS	CompCor, 6 MP and head motion velocity	SPM8, CONN	No	No	Bilateral DLPFC and ventral striatum	Relation between SBC and executive attention and emotional regulation	Double dissociation: ↓ FC between R DLPFC and R dorsal caudate associated with deficits in executive attention but not in emotional regulation; ↓ FC between L ventral striatum and hippocampus, OFC; R ventral striatum and anterior PFC related to deficits in emotional regulation but not executive attention	18	Supports dual-pathway model of ADHD of dissociable cognitive and emotional deficits
Sato (89)	2013	159	12.2	3.3	479	12.2	3.3	ADHD-200 (sites not specified)	N/A	N/A	6 MP, CSF, WM signals	Athena, in-house pipeline	No	No	351 ROIs, subset of Craddock 400 parcellation	Graph spectral entropy	Graph spectral entropy ↑ in ADHD in pre- and postcentral gyrus, STG and IFG	8	Entropy used to quantify greater network disorganization in ADHD; found more sensitive in revealing group differences than other graph theory indices
Sokunbi (88)	2013	17	29.7	10.2	13	29.7	8.4	5min	N/A	N/A	N/A	SPM8; sample entropy algorithm	No	No	WBA	Sample entropy	↓ sample entropy (complexity) in ADHD in SFG, ACC, precuneus, cuneus	13	Small samples; entropy index applied to time series; indicated lower complexity in ADHD
Wang (79)	2013	23	35.1	9.7	23	32.0	9.2	6min 24s	Open	3mm or 3°	6 MP, CSF, WM signals	Athena pipeline scripts; AFNI, FSL	No	No	WBA	ReHo to classify ADHD vs. controls in NYU data shared by 1000 Functional Connectomes	↑ ReHo in bilateral occipital lobes and L frontal lobe in ADHD. Classification accuracy 80%	21	Small sample results with leave one out cross-validation; may not replicate

		ADHD			Controls					Motion Inclusion Criteria	Preprocessing							
* Author	Year	N	Age	SD	N	Age	SD	Scan Duration	Eyes		Nuisance Covariates	Software, pipeline, if specified	Scrubbing? Threshold	GSR	Regions-of-interest	Method or index	Results Related to Intrinsic Brain Activity	GS Cites	Comments
Anderson (46)	2014	276	12.4	-	472	12.4		7 sites from ADHD-200	Both	N/A	6 MP, CSF, WM signals	Athena pipeline scripts; AFNI, FSL	No	No	Multi-modal features including FC matrices	Non-negative matrix factorization	Latent “topics” across phenotypic, behavioral, structural and FC features identified the topic comprising DMN components as differing by diagnosis, although motion parameters and site also contributed	17	“Dismal classification accuracy” ascribed to many factors including marked heterogeneity across sites
de Celis Alonso (81)	2014	23	9.3	2.8	23	9.3	3.5	7min 25s	Closed	3.5mm or 3°	6 MP, CSF, WM signals	DPARSF	0.5mm	No	WBA	ReHo, ALFF and ICA	↓ ReHo in precuneus, cuneus, L mid-occipital cortex, R putamen, L lingual and ventral pallidum; ↑ ReHo in cerebellum and PFC in ADHD	8	1.5 T scanner used; brief session completed in < 15min; structural scans reported to use 0.36×0.36×4mm voxels; results difficult to assess because of apparent errors
Dey (48)	2014	487	N/A	N/A	307	N/A	N/A	4 sites from ADHD-200	Both	No	6 MP, CSF, WM signals	AFNI, FSL, Athena	No	No	Craddock 200 parcellation	Multi-dimensional scaling used to project network properties to a two-dimensional space on which SVM operated	High classification accuracies on training (70%) and test datasets (74%) reported when performed separately on males and females	2	Novel method for reducing data dimensionality
dos Santos Siqueira (49)	2014	269	11.6	2.9	340	11.6	2.9	5 sites from ADHD-200	Both	No	6 MP, CSF, WM signals	Athena	No	No	Craddock 400 parcellation	Graph theoretical measures, SVM	Site-by-site analyses produced wide range of results, e.g., accuracy ranged from 42% to 73% for weighted betweenness centrality	4	Results null in sample as a whole; significant prediction observed in a single site; balanced sample (patients and controls) speculated as basis
Elton (50)	2014	155	11.7	2.5	145	11.8	2.3	3 sites from ADHD-200	Both	No	6 MP, CSF, WM, global signals	AFNI	0.5mm or 0.5% (DVARS)	Yes	Dorsal attention, salience, executive control and default networks; ADHD symptom ratings rescaled to max 1.0	SBC	After accounting for dimensional relationships that were congruent across groups, categorical effects of ADHD diagnosis on FC observed in DMN, salience network and executive control network	10	Replicated and extended Chabernaud 2012 that categorical, dimensional, and categorical by dimensional interactions observed
Hoekzema (118)	2014	22	32.8	10.8	23	29.3	8.9	4min	Open	3mm or 3°	6 MP; CompCor	SPM8, GIFT, CONN	No	No	DMN	ICA and SBC in medication-naïve adults	↑ FC of L IFG with DMN in ADHD; FC was positive in ADHD, negative in controls	34	1.5 T scanner used; peak reported as “ventrolateral part of L DLPFC” but MNI coordinates -48, 26, 4 are in IFG (BA 45); interpreted as decreased segregation in ADHD
Hulvershorn (131)	2014	63	9.4	2.0	19	10.5	1.9	6min 34s	Both	Max displacement > 3mm or mean FD > 0.25mm	6 MP, CSF, WM, global signals	AFNI, FSL	No	Yes	Amygdala	SBC w/ emotional lability ratings	↑ emotional lability associated with ↑ positive FC between amygdala and rostral ACC in ADHD	22	Effects evident after controlling for inattention or hyperactivity/impulsivity
Karalunas (129)	2014	247	9.2	1.3	190	8.3	1.1	7-10min	Open	1.5mm RMS	6 MP, CSF, WM, global signals	In-house pipeline	0.5mm	Yes	WBA, amygdala seed	Community detection analyses based on matrix of child-by-child correlations	Amygdala FC differences contributed to validating subgroups within ADHD; among 39 children with ADHD, 18 classified as mild, 11 as surgent, and 10 as irritable	32	Tour-de-force depicting novel means of phenotyping based on physiology; however, imaging data only available for 39 children with ADHD and 15 controls; represents proof-of-concept pending replication
Kessler (51)	2014	133	11.9	2.8	228	12.8	3.2	7 sites from ADHD-200	Both	≤2SD+mean and ≥40% of volumes remaining after scrubbing	6 MP, top 5 principal components extracted from WM and CSF masks	SPM8	0.2mm	No	DMN, task-positive network (TPN)	Pearson correlations, Joint ICA	↓ DMN-TPN segregation co-occurring with structural abnormalities in dorsolateral PFC and ACC along with abnormal intranetwork FC in DMN, dorsal attention and visual networks	8	Selection criteria retained ~56% of available participants; same strategy used for Sripada (2014 a,b); first study to detect multi-modal structural and FC abnormalities in ADHD
Kong (24)	2014	102	12.1	2.0	143	11.4	1.9	8min	Closed	2SD + group mean	6 MP, CSF, WM, global signals	AFNI, FSL	No	No	WBA	ALFF; head motion regressed out	Head motion in scanner in 566 adults, measured in DTI data, and in 217 children, measured from R-fMRI data, associated with impulsivity trait. When head motion regressed out, ADHD and controls did not differ after correction for multiple comparisons	11	Provocative suggestion that head motion can be both source of artifact and reflect
Li (84)	2014	33	10.1	2.6	32	10.9	2.6	6min 40s	Closed	2mm or 2°	6 MP, CSF, WM, global signals	SPM8	No	Yes	WBA	ALFF	↓ ALFF in L PFC and L ventral SFG, ↑ ALFF in bilateral pallidum and R dorsal SFG; ↑ FC in frontostriatal circuits, ↓ FC in long-range frontoparietal and frontocerebellar networks	14	Stimulant naïve patients; solid methodology
Lin (92)	2014	19	34.9	9.8	18	34.7	9.2	6min 24s	N/A	N/A	CSF, WM signals	AFNI, FSL	No	No	108 based on AAL	Pearson correlations, graph theory (number of nodes and edges), network topological properties	ADHD group had ↓ global efficiency, ↑ local efficiency, longer shortest path, ↑ modularity and ↑ clustering; interpreted as ↓ brain network integration and ↑ brain network segregation in ADHD	3	Data from NYU sample; subset of Castellanos 2008 (97), Uddin 2008 (98); downloaded from 1000 Functional Connectomes (128); unclear if results would have been altered if head micromotion had been quantified
Mattfeld (111)	2014	35	28.4	5.7	17	28.7	4.0	6min	Open	3SD+mean or 0.5mm mean FD	6 MP and first derivatives; aCompCor	SPM8, CONN	No	No	PCC and MPFC seeds from Castellanos 2008 and Fair 2010	SBC	Positive PCC-MPFC FC reduced only in 13 patients with persistent ADHD; negative MPFC-DLPFC FC reduced in both persistent and remitted (n=22) patients	17	Patients with ADHD diagnosed in childhood; explicit replication of Castellanos 2008 (97) & Sun 2012 (100)

		ADHD			Controls					Motion Inclusion Criteria	Preprocessing							
* Author	Year	N	Age	SD	N	Age	SD	Scan Duration	Eyes		Nuisance Covariates	Software, pipeline, if specified	Scrubbing? Threshold	GSR	Regions-of-interest	Method or index	Results Related to Intrinsic Brain Activity	GS Cites	Comments
McLeod (136)	2014	21	12.5	2.9	23	11.3	2.8	5min	Open	N/A	6 MP, CSF, WM signals	FSL	No	No	Motor network	SBC w/ motor network in ADHD comorbid with developmental coordination disorder	↓ FC between primary motor cortex and bilateral IFG, R supramarginal gyrus, angular gyri, insular cortex, amygdala, putamen, and pallidum in patients vs. controls	23	Demonstrated feasibility; findings are admittedly preliminary
Ou (145)	2014	23	N/A	N/A	45	N/A	N/A	N/A	N/A	N/A (6 excluded)	N/A	FSL, in-house pipeline	No	No	358 Dense Individualized and Common Connectivity-based Cortical Landmarks	Bayesian connectivity change point modeling	Atomic Functional Interacting Patterns introduced as novel method based on detecting sudden transitions in network interactions; 94% classification accuracy reported on 5-fold cross-validation; key network features include group differences in interhemispheric FC in prefrontal (↑ in ADHD, ↓ in controls) and dACC (↓ in ADHD than in controls)	4	Age range 8-14 yrs; mean±SD not provided; mathematically complex albeit rigorous approach; unclear how computationally accessible the approach would be for most investigators
Posner (133)	2014	30	9.8	2.1	31	10.8	2.0	5min	Closed	N/A (7 excluded)	No	SPM8, CONN, Artifact Detection Toolbox	Yes	Yes	WBA, hippocampus seed	SBC and association between FC and depression symptoms	↓ FC between L hippocampus and L OFC in ADHD vs. controls; also inversely correlated with depression symptoms in ADHD, as were L hippocampal volumes	8	Depressive symptoms relatively mild in most of the sample; longitudinal follow-up likely to be important to determine significance of the results
Ray (95)	2014	19	N/A	N/A	19	N/A	N/A	3 * 5min (after scrubbing, ~11min)	N/A	< 50% frames removed and > 5min data remaining	6 MP, CSF, WM, global signals	In-house pipeline	0.3mm	Yes	219 cortical regions	Rich-club networks, three-group comparison (autism vs. ADHD vs. controls)	ADHD did not differ from controls in rich-club network FC. Within rich-club networks, FC ↓ for ADHD compared with autism (n=16)	22	Age range 7-13; mean±SD not provided in main text, and Supporting Information Table not available; proof-of-principle that autism and ADHD can be distinguished
Sripada (54)	2014	133	12.0	2.9	288	12.8	3.2	7 sites from ADHD-200	Both	≤2SD+mean and ≥40% of volumes remaining after scrubbing	6 MP, top 5 principal components extracted from WM and CSF masks	SPM8, DARTEL, FSL	0.2mm	No	907 densely distributed ROIs located within Yeo-Krienen 2011 seven large-scale networks	Pearson correlations, network contingency analysis	ADHD exhibited diminished anticorrelation between DMN and anterior insula, SMA; DMN hypoconnectivity; altered FC between DMN and ventral attention, frontoparietal, and visual networks. Abnormalities predominantly right lateralized	33	Based on same subset of ADHD-200 as Kessler 2014 (46) and Sripada 2014 (102); diminished anticorrelation, despite lack of GSR, replicates Castellanos 2008 (97) and Fair 2010 (110); DMN hypoconnectivity replicates Uddin 2008 (98) and Fair 2010 (110)
Sripada (113)	2014	133	12.0	2.9	288	12.8	3.2	7 sites from ADHD-200	Both	≤2SD+mean and ≥40% of volumes remaining after scrubbing	6 MP, top 5 principal components extracted from WM and CSF masks	SPM8, DARTEL, FSL	0.2mm	No	907 densely distributed ROIs located within Yeo-Krienen 2011 seven large-scale networks	Pearson correlations, maturational lag estimated for each functional connection; controls from ABIDE also used to confirm putative age effects	Results consistent with maturational lag in connections within DMN and in DMN interconnections with two task positive networks (frontoparietal and ventral attention networks) in ADHD	22	Leveraged age-related differences in FC strength in large, albeit cross-sectional datasets; reported results represent hypothesis to be confirmed in longitudinal studies
Tomasi (56)	2014	203	12	3	402	12	3	6 sites from ADHD-200	Both	≥75% of volumes remaining after scrubbing	6 MP; voxels with poor SNR eliminated	SPM2	0.5mm or 0.5% (DVARS)	No	Ventral tegmental area, substantia nigra	Pearson correlations, orthogonalized to isolate unique variance for each seed	↑ ventral tegmental area FC with thalamus, subthalamic nucleus, globus pallidus, and ↑ substantia nigra FC with L amygdala and insula in children with ADHD	27	Age-related differences also noted from contrasts with healthy adults from 1000 Functional Connectomes (128); despite large samples, should be interpreted as preliminary until confirmed longitudinally
Barber (117)	2015	50	9.8	1.3	50	10.0	1.0	5min 20s	Open	3mm or 3°	CSF, WM signals, CompCor	SPM8, in-house pipeline	N/A	No	Cingulo-opercular network and DMN	SBC; diagnoses & RT variability indices	ADHD exhibited ↑ FC within cingulo-opercular network and within DMN; ↑ anticorrelation between DMN and occipital regions associated with ↓ RT variability; ↑ anticorrelation between DMN and R lateral PFC associated with ↓ omission errors; distinct brain-behavior relationships also found in diagnostic groups	2	First study to include RT variability indices, coefficient of variation and tau, as well as omission error rate; substantial sample size; comorbidity other than oppositional defiant disorder excluded; 35 of 50 children with ADHD medicated, with 48 hour washout; only medicated children showed anticorrelation between DMN and cingulo-opercular network, interpreted as potentially reflecting compensatory effect
Carmona (98)	2015	120	12.1	2.2	120	12.0	2.2	5 sites from ADHD-200	N/A	0.5mm FD	6 MP, CSF, WM, global signals	AFNI, FSL, Athena	0.5mm	Yes	Sensory, attentional and higher-order cognitive circuits	Stepwise functional connectivity (SFC)	ADHD exhibited ↓ SFC to executive processing areas and ↑ SFC to DMN regions	1	Novel network approach based on modeling FC as series of discrete relays, or link-step distances
Francx (120)	2015	129	17.6	2.8	100	17.1	3.0	9min	Open	Visual inspection; 0.73mm RMS	ICA-AROMA; CSF, WM signals	FSL, ICA-AROMA	No	No	Executive control, cerebellum, nucleus accumbens, caudate and putamen networks	SBC	↓ ADHD symptoms in longitudinal follow-up related with ↑ FC within ACC and paracingulate gyrus; no significant effects of subcortical networks	1	ICA-AROMA preprocessing asserted to enhance removal of motion artifacts; results interpreted as supporting hypothesis that ADHD symptoms remit as function of maturation of PFC networks
Ho (132)	2015	15	9.4	1.2	12	10.3	2.3	4min 6s * 2	Open	90% of frames remain	N/A	SPM8, DARTEL, GIFT	0.5mm FD & DVARS >6.5%	No	Affective/limbic network	ICA-based identification of affective network	ADHD demonstrated ↓ integrated affective network (↑ bilateral amygdalar and ↓ L OFC connectivity with entire affective network) ↑ L amygdalar FC with the affective network was associated with ↑ aggressiveness and conduct problems in ADHD	0	Small sample sizes; 10 patients rescanned 3 months later; similar effects observed in this subset, consistent with their representing traits

		ADHD			Controls					Motion Inclusion Criteria	Preprocessing							
* Author	Year	N	Age	SD	N	Age	SD	Scan Duration	Eyes		Nuisance Covariates	Software, pipeline, if specified	Scrubbing? Threshold	GSR	Regions-of-interest	Method or index	Results Related to Intrinsic Brain Activity	GS Cites	Comments
Hong (135)	2015	83	9.6	2.6	22	9.8	2.6	6min 24s	Closed	2mm or 2°	6 MP, CSF, WM, global signals	SPM8	No	Yes	Bilateral dorsal and ventral caudate, dorsal-caudal putamen and ventro-rostral putamen	SBC comparison between ADHD and TD, and between good-responders and poor-responders to methylphenidate; CPT errors	↓ FC between dorsal caudate and L superior frontal and R middle frontal cortex in ADHD; ↓ FC between ventral caudate with R rectal gyrus and R OFC in good-responders vs. poor-responders; striatal FC also related to CPT errors	4	Only positive FC examined because of concerns regarding GSR; medication response used to stratify ADHD group, suggesting therapeutic mechanism
Kucyi (115)	2015	23	24.3	3.9	23	24.2	2.9	10min 8s	Open	N/A	aCompCor, 6 MP, CSF, WM signals	FSL, fMRISTAT	No	No	Cerebellar DMN seed	SBC	↑ FC between cerebellar DMN and multiple networks, particularly visual, dorsal attention, salience, and sensorimotor in ADHD	4	Highlights relevance of cerebellar FC, which was previously ignored in ADHD
Lin (141)	2015	25	9.9	1.8	25	10.0	2.1	6min	Closed	1mm max FD	Multiple approaches, Friston-24, CSF, WM, global signals; also without GSR; CompCor	DPARSF, CONN	0.5mm	Yes	Canonical seeds of the frontoparietal control network in anterior PFC	Whole brain SBC	↓ FC between R anterior PFC and R ventrolateral PFC was robust to all 3 preprocessing strategies; ↓ FC between L anterior PFC and R inferior parietal lobule also found; these abnormalities related with oppositionality and impulsive symptoms, respectively	0	Highlights frontoparietal executive control network; moderate sample size
Sidlauskaite (143)	2015	19	29.8	9.6	23	27.2	8.7	6min	Closed	N/A	aCompCor: motion, CSF, WM signals	SPM8, CONN	No	No	Anatomic regions corresponding to DMN, ventral attention, dorsal attention, and salience networks	SBC	↑ FC found in ADHD between the two attention networks and within DMN and ventral attention network; salience network was hypoconnected to dorsal attention network in ADHD	1	Moderate sample sizes; highlights interplay among attention, salience and default networks per Menon 2011 tri-network hypothesis (114), although nomenclature may confuse
Somandepalli (100)	2015	46	11.4	3.1	57	12.5	3	6min	Both	Mean FD < 0.2mm	Friston-24, CSF, WM signals; also CompCor & with global signal	C-PAC	No	No	WBA	Intra-class correlations (ICC) for ALFF, fALFF, ReHo, voxel-mirrored homotopic connectivity, and PCC FC	ICC acceptable for all indices and mostly comparable across groups; circumscribed regional group differences always indicated ↓ reliability in ADHD	2	Examination of short-term (intrasession) test-retest reliability; results are mostly reassuring, but point to continuing importance of quantifying reliability, especially at longer intervals
Wang (57)	2015	36	11.0	2.7	35	11.8	2.9	5min 52s	Closed	3mm and 3° and < 20% "outlier" frames	6 MP, Friston-24, CSF, WM, global signals	AFNI, FSL	No; FD> 0.5mm defined as "outliers"	Yes	20 networks from Biswal (2010)	ALFF, Pearson correlations and absolute value of negative correlations	ADHD exhibited ↑ network-wise ALFF in attention and default mode network; altered FC also observed in ADHD; ALFF also related to magnitude of FC correlations, inattention scores and performance IQ	0	Data downloaded from NYU ADHD-200 contribution; moderate sample sizes; results not controlled for multiple tests performed; novel element is joint examination of amplitude and FC; biological meaning unclear
Yu (80)	2015	30	10.2	1.7	30	10.3	1.7	8min	Closed	3mm or 3°	Friston-24, CSF, WM, global signals	DPARSF	No	Yes	WBA	Frequency-based analysis of ReHo	Significant interactions reported between frequency band and diagnosis in bilateral OFC, DLPFC, SFG, and L postcentral gyrus, parietal cortex, R fusiform, L thalamus, and R anterior cerebellum	0	Theoretical limit of spectral resolution is about 0.008 Hz, which is near frequency band (< 0.01 Hz) in which the greatest between-group differences were found
Zhang (86)	2015	239	11.5	2.5	251	11.8	2.5	2 sites from ADHD-200	Both	1.5mm or 1.5°	6 MP, CSF, WM, global signals	DPARSF	No	Yes	90 AAL regions	Triplet-ROI-based partial correlation to identify primary mediating regions for each pair of ROIs	Most affected edges in ADHD included OFC, inferior and superior frontal gyrus, ACC, PCC, calcarine cortex and parahippocampus; across all 3 disorders, opposite hemisphere counterparts contribute 60–76% of variance to altered FC	3	Compared ADHD, major depression and schizophrenia; highlights the intriguing robustness of intrinsic homotopic synchrony and suggests that altered interhemispheric communication/integration may be a common motif in psychopathology
Cai (47)	2016	90	11.4	N/A	90	11.4	N/A	3 sites from ADHD-200	Both	1 voxel	N/A	SPM8, MELODIC	0.2mm	No	Salience network (SN), central executive network (CEN) and DMN	Resource allocation index (RAI; difference in correlation between SN and CEN time series, and correlation between SN and DMN time series)	↓ RAI in ADHD, indicating ↓ cross-network interactions among SN, DMN, and CEN	0	Ingenious approach leveraging availability of open data to test replicability of the Menon 2011 tri-network hypothesis (114); highlights cross-network interactions as opposed to individual network differences, which did not replicate across sites
Rosenberg (144)	2016	38	11.8	N/A	75	11.8	N/A	1 site from ADHD-200	Both	0.06mm FD	6 MP, CSF, WM, global signals	SPM8, in-house (BioImage Suite)	No	Yes	236-region functional parcellation (Shen, 2010)	Pearson correlations; index of sustained attention (d' values) from novel CPT	Performance on sustained attention task used to identify high- and low-attention networks from task-fMRI data in 25 young adults; same networks also predicted sustained attention performance in resting state data from the same adults; same networks predicted ADHD ratings in resting data from an independent sample of children and adolescents	1	Availability of ADHD-200 allowed extension to a completely independent dataset; the data-driven derived Sustained Attention Network model comprised "wide swaths of cortex ... subcortical regions and cerebellum" rather than being limited to frontoparietal regions; data-driven method theoretically applicable to broad range of cognitive and clinical measures

Abbreviations: AAL: Automated Anatomical Labeling atlas; ABIDE: Autism Brain Imaging Data Exchange; ACC: anterior cingulate cortex; aCompCor: anatomical CompCor; ADHD-C: ADHD combined type; ADHD-I: ADHD inattentive type; ADHD: attention-deficit/hyperactivity disorder; AFNI: Analysis of Functional NeuroImages; ALFF: amplitude of low-frequency fluctuations; Athena: ADHD-200 Preprocessed Initiative; BA: Brodmann area; BOLD: blood-oxygen-level dependent; C-PAC: Configurable Pipeline for the Analysis of Connectomes; CompCor: Control of physiological/movement effects; CONN: Functional Connectivity Toolbox; CPT: Continuous Performance Test;CSF: cerebrospinal fluid; dACC: dorsal ACC; DARTEL: Diffeomorphic Anatomical Registration Through Exponentiated Lie

Algebra; DLPFC: dorsolateral prefrontal cortex; DMN: default mode network; DPARFS: Data Processing Assistant for Resting-State fMRI; DTI: diffusion tensor imaging; DVARS: term referring to the temporal derivatives of timecourses, referenced to the RMS signal change calculated over the whole brain; EPI: echo planar imaging; fALFF: fractional ALFF; FC: functional connectivity; FD: framewise displacement; fMRI: functiona MRI; fMRISTAT: a Matlab toolbox for the statistical analysis of fMRI data; FSL: FMRIB Software Library; GIFT: Group ICA of fMRI Toolbox; GS Cites: Google Scholar Citations on Feb 3, 2016; GSR: global signal regression; ICA-AROMA: ICA-based strategy for Automatic Removal of Motion Artifacts; ICA: independent component analysis; IFG: inferior frontal gyrus; IQ: intelligence quotient; ITG: inferior temporal gyrus; MELODIC: Multivariate Exploratory Linear Optimized Decomposition into Independent Components; MFC: medial frontal cortex; MFG: middle frontal gyrus; MNI: Montreal Neurological Institute; MP: motion parameters; MRI: magnetic resonance imaging; MTG: middle temporal gyrus; N/A: not available; NYU: New York University; OFC: orbitofrontal cortex; PCA: principal component analysis; PCC: posterior cingulate cortex; PFC: prefrontal cortex; RDoC: Research Domain Criteria; ReHo: regional homogeneity; REST: Resting-State fMRI Data Analysis Toolkit; RMS: root mean square; ROI: region of interest; RT: reaction time; SBC: seed based correlation; SD: standard deviation; SFG: superior frontal gyrus; SMA: supplementary motor area; SNR: signal-to-noise ratio; SPM: Statistical Parametric Mapping; STG: superior temporal gyrus; SVM: support vector machine; TR: repetition time; WBA: whole brain analysis; WM: white matter

*Citation number in bibliography