Is the ADHD Brain Wired Differently? A Review on Structural and Functional Connectivity in Attention Deficit Hyperactivity Disorder

Kerstin Konrad,[1,2,3]* and Simon B. Eickhoff[2,3,4]

[1]*Child Neuropsychology Section, Department of Child and Adolescent Psychiatry and Psychotherapy, University Hospital of the RWTH Aachen, Germany*
[2]*Institute of Neuroscience and Medicine (INM-2, INM-3), Research Center Juelich, Germany*
[3]*JARA – Translational Brain Medicine, Germany*
[4]*Department of Psychiatry and Psychotherapy, University Hospital of the RWTH Aachen University, Germany*

Abstract: In recent years, a change in perspective in etiological models of attention deficit hyperactivity disorder (ADHD) has occurred in concordance with emerging concepts in other neuropsychiatric disorders such as schizophrenia and autism. These models shift the focus of the assumed pathology from regional brain abnormalities to dysfunction in distributed network organization. In the current contribution, we report findings from functional connectivity studies during resting and task states, as well as from studies on structural connectivity using diffusion tensor imaging, in subjects with ADHD. Although major methodological limitations in analyzing connectivity measures derived from noninvasive in vivo neuroimaging still exist, there is convergent evidence for white matter pathology and disrupted anatomical connectivity in ADHD. In addition, dysfunctional connectivity during rest and during cognitive tasks has been demonstrated. However, the causality between disturbed white matter architecture and cortical dysfunction remains to be evaluated. Both genetic and environmental factors might contribute to disruptions in interactions between different brain regions. Stimulant medication not only modulates regionally specific activation strength but also normalizes dysfunctional connectivity, pointing to a predominant network dysfunction in ADHD. By combining a longitudinal approach with a systems perspective in ADHD in the future, it might be possible to identify at which stage during development disruptions in neural networks emerge and to delineate possible new endophenotypes of ADHD. *Hum Brain Mapp 31:904–916, 2010.*

Key words: connectivity; ADHD; fMRI; DTI

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is one of the most common childhood neuropsychiatric disorders, and it often persists into adulthood. The psychopathology of this disorder is marked by developmentally inappropriate and pervasive expressions of inattention, overactivity, and impulsiveness. ADHD is also associated with functional impairments across multiple academic and social domains and is commonly accompanied by a range of

Contract grant sponsor: German Federal Ministry of Education and Science (for K.K.); Contract grant numbers: BMBF-EDNET-01GV0602, BMBF-ANAC-01GJ0808; Contract grant sponsor: Human Brain Project (for S.B.E.); Contract grant number: NIH R01-MH074457-01A1; Contract grant sponsors: Excellence Initiative of the German federal and state governments (JARA-Seed fund) for K.K.; the Helmholz Initiative on Systems-Biology "The Human Brain Model" for S.B.E.

*Correspondence to: Kerstin Konrad, Child Neuropsychology Section, Department of Child and Adolescent Psychiatry and Psychotherapy, University Hospital of the RWTH Aachen, Germany. E-mail: kkonrad@ukaachen.de

Received for publication 31 October 2009; Revised 17 February 2010; Accepted 4 March 2010

DOI: 10.1002/hbm.21058

Published online 3 May 2010 in Wiley InterScience (www.interscience.wiley.com).

externalizing and internalizing disorders [Biederman and Faraone, 2006]. Given the associated burden to society, family and the individual child, understanding the causes of ADHD and developing new and more effective treatments targeting these underlying causes is an important goal for neuroscience research.

Although neuroimaging studies clearly point to a neurobiological basis for the disorder, the pathophysiological mechanisms of ADHD and the specific nature of the atypical brain development underlying it remain poorly understood. Recently, in concordance with emerging concepts in other neuropsychiatric disorders such as schizophrenia and autism, a change in perspective in etiological models of ADHD has occurred. These models shift the focus of the assumed pathology from regional brain abnormalities to dysfunctions in distributed network organization [Sergeant et al., 2006]. While the assessment of functional segregation in the human brain, i.e., the localization of regionally specific functions, has been the predominant concept in imaging neuroscience for many years, the pathophysiology of neuropsychiatric disorders is now being increasingly treated from a systems perspective in which function emerges from an interaction of regionally specialized elements. As a result, the analysis of brain connectivity has become more and more critical. However, the analysis of each of the three fundamental aspects of brain connectivity, namely, anatomical, functional and effective connectivity, is associated with its own technical and conceptual challenges.

In the current review, we aim to integrate findings from functional connectivity studies during resting and task states with those from studies on structural connectivity. After a description of different connectivity methods and a critical discussion of methodological challenges and limitations associated with each of these measures, we will briefly summarize the typical development of cortical connectivity patterns across the human lifespan and then discuss the findings of atypical brain connectivity in subjects with ADHD. Finally, we will discuss how a systems perspective might impact our understanding of the development of ADHD pathology and how such a systems perspective can be addressed in future connectivity studies of this disorder.

Connectivity Measures

Functional connectivity during resting state and during tasks using functional magnetic resonance imaging

Functional connectivity is defined as the temporal correlation or coherence of spatially remote neurophysiological events. In resting-state fMRI, which is defined by the absence of external perturbations, stimulus-locked averaging of responses is not applicable. This leads to the development of new analytical approaches for the assessment of functional connectivity.

Using resting state fMRI, the so-called default-mode network (DMN), a large and robustly replicable network of brain regions that is associated with task-irrelevant mental processes and mind wandering, has been identified. The DMN comprises the precuneus/posterior cingulate cortex (PCC), the medial prefrontal cortex (MPFC) and the medial, lateral, and inferior parietal cortex [Laird et al., in press; Schilbach et al., 2008]. The DMN shows higher activity and stronger functional connectivity during rest than during externally driven tasks [Raichle et al., 2001]. Activity in the DMN is attenuated, although not extinguished, during the transition from rest-to-task states (Eichele et al., 2008; Greicius and Menon, 2004], and stronger deactivation is associated with increased task difficulty [Singh and Fawcett, 2008]. Persistence of DMN activity during tasks has been shown to predict errors in the flanker [Eichele et al., 2008] and the stop signal task [Li et al., 2007]. Moreover, unsuccessful attenuation of the DMN has also been reported to be associated with momentary lapses in attention denoted by longer reaction times (RTs) and less accurate performance in an attentional control task [Weissman et al., 2006]. Hence, a failure to sufficiently suppress DMN activity may result in excessive DMN activity that interferes with performance on tasks [Li et al., 2007].

Regions of the DMN show strong functional (temporal coherence of BOLD signal in fMRI; Fox and Raichle, 2007] and structural connectivity (fiber tracking based on DTI; Grecius et al., 2008]. Consequently, there is considerable evidence, though no unequivocal proof, for structured exchange of information between the different DMN regions [Buzsáki and Draguhn, 2004; Laird et al., in press]. On the basis of these findings and on the apparent antagonism between its activation and task performance, the DMN can be conceptualized as a strongly interconnected task-negative network.

In addition to the DMN, a second prominent network has been characterized by spontaneous low frequency activity. Unlike the DMN, this network, which includes the dorsolateral prefrontal cortex (DLPFC), the intraparietal sulcus (IPS), and the supplementary motor area (SMA), has been described as task-positive, i.e., showing more activity during tasks that require active allocation of attentional resources than during rest. These regions therefore appear to be associated with increased alertness, response preparation and selective attention in a manner that is largely independent of the specific task at hand [Fox et al., 2005; Sonuga-Barke and Castellanos, 2007]. Interestingly, the task-positive fronto-parietal network and the DMN are temporally anti-correlated, such that task-specific activation of the task-positive network is associated with attenuation of the DMN and vice versa.

Despite recent advances in resting-state fMRI data analysis, it should be noted that an important limitation of the widely applied correlation approach is the inherently

subjective choice of the seed region of interest (ROI) by the investigator. Furthermore, in the correlation approach the global signal is usually regressed out. The use of such a preprocessing step can induce false negative correlations between brain regions [Murphy et al., 2009]. To avoid these issues, data-driven approaches such as independent component analysis (ICA) have become increasingly prevalent in the analysis of resting-state data. ICA decomposes the four-dimensional (i.e., brain volume over time) blood oxygen level dependent (BOLD) signal into a set of spatially distinct maps and their associated time courses. Among these independent components are several reliably identified functional brain networks, but also artifacts related to movement and physiological noise [Beckmann et al., 2005]. A general limitation of resting-state fMRI is that it is very difficult to separate physiological noise from the BOLD signal of interest. Independent component analysis largely separates these signals; however, residual noise may still be present in the components of interest [Birn et al., 2008]. A possible solution to this problem is to collect physiological measurements, model the evoked signal changes and remove these confounds from the fMRI data. Another potential difficulty with the analysis of resting-state fMRI is that resting-state connectivity shows prominent very low frequency (<0.1 Hz) oscillations that are hypothesized to provide temporal synchrony between brain regions (Fox et al., 2006; Sonuga-Barke and Castellanos, 2007]. The physiology of these BOLD fluctuations and their relationship to neuronal activity, however, are a matter of conjecture. These conceptual problems have prompted the need for additional cross-validation of resting-state connectivity. One approach that has provided support for the validity of the ensuing networks [Smith et al., 2009] is the delineation of task-related functional connectivity networks using coordinate-based meta-analysis [Eickhoff et al., 2009a; Laird et al., 2009]. While the congruence between the functional architecture of the brain during the task and at rest is reassuring, further research into the nature and physiology of resting-state networks should add to the validity of these approaches.

Functional connectivity refers to the temporal correlation of spatially remote neurophysiological events. It has been investigated using several different approaches, including seed-voxel correlation analyses, ICAs and meta-analytical connectivity modeling. Interestingly, all of these methods seem to provide evidence for several functional networks in the brain, most prominently the DMN and a fronto-parietal task-positive network. There are, however, also discrepancies between the results obtained using the different methods. These may reflect differential confounds or point to different aspects of brain connectivity being captured. The currently used approaches to functional connectivity share some important drawbacks. These include the danger of the induction of spurious correlations by indirect effects and the fact that type and directionality of interactions cannot be delineated. Another major drawback is that functional connectivity analyses usually do not allow inferences about the context-dependent dynamics of inter-regional interactions. In summary, functional connectivity subsumes a variety of conceptually and technically different approaches that enable the delineation of functional brain networks defined by correlated neuronal activity but do not allow inferences to be made about the causal nature of interactions between individual areas.

Effective connectivity refers to the influence that a particular brain region exerts over another, spatially distant region. Because these effects cannot be directly assessed, inference on effective connectivity always relies on models of interactions; such models are usually informed by knowledge of the structure of the experiment, physiological constraints and other a priori assumptions. After fitting the model to the experimental data, inference is then sought on the parameters capturing the influences between different brain regions. It becomes evident that effective connectivity analysis can provide information about directionality and context-dependent dynamics of interactions that cannot be derived from any other measure of connectivity. As these approaches are highly driven by hypotheses and prior assumptions, however, the validity of the inferences is also crucially dependent on these assumptions. In a complex and yet poorly understood system such as the brain, unequivocally acceptable assumptions are sparse, resulting in competing approaches and a potential dependency of the results on the chosen model. In summary, effective connectivity provides models of brain function that allow mechanistic insight into the causal nature of inter-regional interactions but can do so only by reference to several assumptions and a potential (over)simplification of the network at hand.

Structural connectivity

Anatomical connectivity refers to the presence of an axonal connection between two brain regions. It was historically investigated exclusively in non-human primates using invasive tracing; however, with the advent of diffusion tensor imaging (DTI), it has been the focus of many in vivo imaging studies.

DTI is an imaging technique based on the random diffusion of water molecules [Le Bihan, 2003; Moseley et al., 1990]. In an unrestricted environment, water molecules diffuse freely in any direction. In the white matter, however, diffusion is restricted by the cell membranes and myelin sheath. Consequently, water diffuses more readily along the orientation of axons, i.e., fiber tracts, than perpendicular to the axons. Measuring the direction of diffusivity can therefore be used to infer the orientation of white matter tracts in the brain. Several measures have been developed and can be used to quantify white matter integrity using DTI, the most common being fractional anisotropy (FA), mean diffusivity (MD), fiber count, and probabilistic tractography.

The development of DTI has been an important contribution to the field of neuroimaging, allowing inference

about structural connectivity in vivo. Despite its potential, however, DTI also has several important limitations, including susceptibility-induced signal loss, limited resolution and dependency on the mathematical models used to infer fiber orientation. In particular, due to the resolution of the DTI signal, a given voxel may often include several fiber tracts coursing in multiple directions. This can lead to an incorrect measure of the principal diffusion direction for a particular tract. Moreover, it should be pointed out that, in contrast to invasive techniques, DTI tractography reveals only the likely presence of a fiber tract between two regions, not axonal (i.e., synaptic) connectivity. Likewise, DTI does not allow inference regarding the directionality of a particular tract or the laminar specificity of the input/output neurons, which in turn provide critical constraints for cortical information processing. DTI can thus delineate the task-invariant anatomy of the WM providing the scaffold for any sort of functional interaction but does not allow any inference on the dynamic nature of these interactions.

The relationship between anatomical and functional connectivity is still disputed, and the number of studies directly comparing resting-state functional connectivity to DTI results is still relatively small. Honey et al. [2007] used a computational approach to study spontaneous resting-state fluctuations and their associations with structural connectivity based on invasive tract tracing data from macaque monkeys. They demonstrated that the anatomical configuration of neuronal networks can predict functional connectivity within these networks on multiple timescales. Their work provided the first demonstration that the dynamics of resting-state networks may be determined, at least partially, by anatomical constraints.

Recently, Damoiseaux and Greicius [2009] reviewed eight articles that directly compare resting-state functional connectivity with structural connectivity and three clinical case studies of patients with limited white matter connections between the cerebral hemispheres. The reviewed studies showed largely convergent results, indicating that the strength of resting-state functional connectivity is positively correlated with structural connectivity strength. Functional connectivity was also observed, however, between regions where there is little or no structural connectivity and vice versa. Such divergences between functional and anatomical connectivity may be interpreted in several ways: (i) coactivation of two regions may not be mediated by direct anatomical connections but via additional structures. Such relays could either consist of a single area or, e.g., involve cascades of several intermediate areas or cortical-subcortical loops [Eickhoff et al., 2009b; Grefkes et al., 2008]; (ii) A third area could project (directly) to two regions, inducing a correlation of functional activation between them without a direct anatomical connection. That is, functional connectivity may be driven by an external source that induces concurrent activity in both areas; and (iii) A very weak anatomical connection between two regions may still hold a high functional significance (Eickhoff et al., 2008; Friston, 2002]. One example would be a case in which activity in one area depends on a "go signal" from another region. Functional connectivity is hence strongly influenced not only by the strength of an anatomical connection but also by the information conveyed through it.

The limitations inherent to each of the different methods commonly used to assess brain connectivity, as well as the discrepancies in the inferences that can be derived from each, likely prohibits a full understanding of physiological or pathological networks based on any one approach. On the other hand, information about different aspects of brain connectivity may provide converging or complementary evidence regarding network properties. A deeper understanding of brain connectivity and its ensuing functional networks should thus rely on a combination of different but complementary approaches.

In the following, we will briefly summarize the typical development of brain connectivity before discussing the atypical development of neural network integration in subjects with ADHD.

Typical Development of Brain Connectivity

Fair et al. [2008] showed that the default network structure in children deviates significantly from that seen in healthy adults. Comparable to adults, interhemispheric functional connections between homotopic regions appear to be relatively strong in children. As a whole, however, the DMN is only sparsely connected, i.e., it is more fragmented. During the course of normal brain development, the default network then becomes significantly more integrated until the adult configuration is reached. This suggests a more predominant functional segregation in children and greater functional integration in young adults.

Recent advances in graph theoretical approaches allow the characterization of topological properties of complex networks. Using these approaches, Watts and Strogatz [1998] have shown that graphs with dense local connections and few long connections can be characterized as small-world networks. Small-world network topology has been demonstrated in many complex networks, including social, economical, and biological networks (see Boccaletti et al., 2006 for a review); more recently, small-world topology has also been demonstrated in large-scale structural brain networks in humans and nonhuman primates [Hagmann et al., 2007].

Using this small-world approach, Supekar et al. [2008] recently reported that normal development of functional connectivity is characterized by simultaneous reduction of local circuitry and strengthening of long-range connectivity. Importantly, this study showed that this is a general developmental principle that operates at the level of the entire brain and not just in circumscribed nodes of the attentional control and default mode networks, as

previously demonstrated [Fair et al., 2007, 2008]. Findings are therefore consistent with regard to distributed changes in large-scale network properties during development. Detailed comparison between different studies, however, is difficult due to lack of correspondence between the underlying data structures. Although Supekar et al. [2009] analyzed the connectivity of 90 cortical and subcortical nodes based on a macro-anatomical whole-brain parcellation [Tzourio-Mazoyer et al., 2002], Fair et al. [2007, 2008] focused their analysis on 39 cortical regions implicated in the task-control and default-mode networks. Interestingly, Supekar et al. [2009] showed that the shift in predominant strength from short- to long-range connections is related to the actual anatomical (physical) distance as derived from DTI measurements, rather than to the euclidean distance between nodes. These findings suggest that changes in functional integration and segregation are closely intertwined with wiring distance, which may reflect a general principle of brain development. They also demonstrate that the dynamic process of over-connectivity followed by pruning, which rewires connectivity at the neuronal level, also operates at the systems level.

With respect to the development of structural connectivity, it is known that myelination in the spinal cord begins at around 10 weeks gestation. At birth, the pons and cerebellar peduncles are myelinated, followed by the internal capsule, the splenium of the corpus callosum, the anterior limb and the genu of the internal capsule. Approximately one year after birth, parts of the frontal, parietal and temporal lobes are myelinated [Paus et al., 2001]. In the hippocampus and frontal lobes, however, myelination continues during adolescence and is not completed until early adulthood [Arnold and Rioux, 2001]. Recently, it has been shown that maturation was attained by adolescence in broadly distributed association and projection fibers, including those supporting cortical and brain stem integration that may underlie known enhancements in reaction time that occur during this period. Maturation after adolescence occurred in association and projection tracts, including prefrontal-striatal connections known to support top-down executive control of behavior and interhemispheric connectivity. Maturation proceeded in parallel with pubertal changes to the postpubertal stage, suggesting hormonal influences on white matter development [Asato et al., in press].

Atypical Development of Connectivity in ADHD

DMN in ADHD

The majority of functional imaging studies in patients with ADHD have focused on the use of various cognitive activation paradigms to specifically identify dysfunction of different elements in the neural circuits subserving cognition, attention, and motor functions. Nevertheless, potential disturbances of resting-state networks, in particular the DMN, have received growing interest in the study of ADHD pathophysiology. These studies are based on the hypothesis that one of the causes of ADHD may be dysfunction of or disconnection between brain regions that support the 'default network'. Such misconfiguration of the DMN may result in a reduced capability for modulation of its activity, which in turn may interfere with task-relevant attentional networks, as outlined above.

With respect to the involvement of the DMN in ADHD pathophysiology, two perspectives have been developed. On one hand, different models conceptualize ADHD as a disorder driven by either a hyper [Tian et al., 2006] or a hypoconnectivity of the DMN [Castellanos et al., 2008; Helps et al., 2008]. Thus far, however, results from different studies regarding pathological changes in DMN connectivity are inconsistent. For example, Tian et al. [2008] found that patients with ADHD exhibited higher resting-state activity in lower-level sensory cortices and interpreted these findings as a neural substrate of inattention in ADHD. In contrast, using a similar approach, Castellanos et al. [2008] observed reduced functional connectivity between the anterior cingulate cortex and various nodes of the DMN (precuneus and PCC). The latter authors also reported altered functional connectivity within the default network itself (VMPFC, precuneus, and PCC). In a subsequent study by the same group using a different network homogeneity model, these findings were essentially confirmed [Uddin et al., 2008]. On the other hand, it has been suggested that DMN activity is undisturbed at rest but fails to be attenuated during the transition from rest-to-task in ADHD patients. This persistent DMN activity then intrudes into and interferes with the neuronal circuits underlying active task performance (i.e., the default-mode interference hypothesis; Sonuga-Barke and Castellanos, 2007]. This hypothesis predicts that disturbances in attention due to interference by the DMN would have a distinctive, slowly fluctuating pattern. On the behavioral level, these effects would be mirrored by periodic and transitory performance deficits manifested as, e.g., increases in RT and frequency of errors, with episodic lapses. To date, however, experimental data supporting this hypothesis is sparse and the predictions are yet to be confirmed.

Using small-world network typology, Wang et al. [2009] were able to demonstrate that although the neuronal connectivity patterns of both ADHD and control groups displayed economical small-world properties, the topology of the networks of the ADHD group was altered compared to that of the control group. First, a tendency toward decreased global efficiency of the brain networks was found in ADHD over the whole cost range. Second, the study revealed that nodal efficiency was profoundly affected at several regions of prefrontal, temporal, and occipital cortices in children with ADHD.

Findings from resting-state fMRI studies that include subjects with ADHD are summarized in Table I.

As can be seen, these study results show some inconsistencies that deserve further comment. First, the heterogeneity of findings might reflect differences in methodology

TABLE I. Neuroimaging studies on structural and functional connectivity in subjects with ADHD

Authors	Measures	Task	Subjects	Findings
		Resting state		
Tian et al. (2006)	fMRI, ROI, LFF	Resting state	$N = 8$ subjects with ADHD compared to $N = 8$ controls (aged 11–15 years)	Compared to controls, ADHD patients exhibited more significant resting-state functional connectivities with the dACC in thalamus, cerebellum, insula and pons, all bilaterally. No brain region in the controls was found to exhibit more significant resting-state functional connectivity with the dACC
Cao et al. (2006)	fMRI, seed-based correlation analyses, regional homogeneity	Resting state	$N = 23$ boys with ADHD compared to $N = 21$ controls (aged 11.00–16.5 years)	Boys with ADHD showed decreased regional homogeneity in the frontal-striatal-cerebellar circuits, but increased regional homogeneity mainly in the occipital cortex.
Zhu et al. (2005)	Multivariate pattern classification for ReHo values assessed by fMRI	Resting state	$N = 9$ subjects with ADHD (aged 11–15 years) compared to $N = 11$ controls	Initial experimental results show a successful classification rate of 85%, using leave-one-out cross validation. Compared with linear SVM and Batch Perceptron, the classifier outperformed the alternatives significantly.
Zang et al. (2006)	ALFF (0.01-0.08Hz)	Resting-state	$N = 13$ subjects with ADHD (aged 13 ± 1.4 ears) compared to $N = 12$ controls	Patients with ADHD had decreased ALFF in the right inferior frontal cortex, left sensorimotor cortex, and bilateral cerebellum and the vermis as well as increased ALFF in the right anterior cingulated cortex, left sensorimotor cortex, and bilateral brainstem.
Castellanos et al (2008)	fMRI, ROI	Resting state	$N = 20$ adults with ADHD compared to $N = 20$ controls	Examination of control subjects verified presence of an antiphasic or negative relationship between activity in dorsal anterior cingulate cortex and in default-mode network components. Group analyses revealed ADHD-related compromises in this relationship, with decreases in the functional connectivity between the anterior cingulate and precuneus/posterior cingulate cortex regions. Secondary analyses revealed an extensive pattern of ADHD-related decreases in connectivity between precuneus and other default-mode network components, including-ventromedial prefrontal cortex and portions of posterior cingulate
Tian et al. (2008)	fMRI, ROI, RSAI	Resting state	Same dataset as Tian et al. (2006)	As compared to the controls, the ADHD patients exhibited more significant resting-state activities in basic sensory and sensory-related cortices.

TABLE I. (Continued)

Authors	Measures	Task	Subjects	Findings
Uddin et al. (2008)	fMRI, network homogeneity	Resting state	Same dataset as Castellanos et al. (2008)	Reduced network homogeneity within the default mode network in ADHD subjects compared to age-matched controls, particularly between the precuneus and other default mode network regions
Helps et al (2008)	DC-EEG, VLFO (<0.2 Hz)	Resting state	13 young adults with high- compared to 11 adults with low self-ratings of ADHD	A consistent and temporally stable pattern of VLFOs was observed across specific scalp regions in low-ADHD participants. High-ADHD participants had less VLFO power across these locations, especially where inattention self-ratings were high. Inattention was not related to VLFO power in other locations
Wang et al. (2009)	Correlation matrix between 90 cortical and subcortical regions, further analyzed by applying graph theoretical approaches (small world network topology)	Resting state	$N = 19$ subjects with ADHD (aged 13.59 ± 1.52 years) compared to $N = 20$ controls (aged 13.32 ± 0.97 years)	Increased local efficiencies combined with a decreasing tendency in global efficiencies found in ADHD suggested a disorder-related shift of the topology toward regular networks. Additionally, significant alterations in nodal efficiency were also found in ADHD, involving prefrontal, temporal, and occipital cortex regions
		Cognitive Tasks		
Wolf et al. (2009)	fMRI, ICA	Working memory task	$N = 12$ adults with ADHD compared to $N = 12$ controls	In both groups, independent component analyses revealed a functional network comprising bilateral lateral prefrontal, striatal, and cingulate regions. ADHD adults had significantly lower connectivity in the bilateral VLPFC, the anterior cingulate cortex, the superior parietal lobule, and the cerebellum compared with healthy controls. Increased connectivity in ADHD adults was found in right prefrontal regions, the left dorsal cingulate cortex and the left cuneus
Rubia et al. (2009)	fMRI, correlation of averaged time-series	Rewarded continuous performance test	N =13 treatment-naive subjects with ADHD (aged 10–15 years) scanned twice (on and off medication) compared to $N = 13$ controls	Under placebo, patients with ADHD showed reduced activation and functional interconnectivity in bilateral fronto-striato--parieto-cerebellar networks during sustained attention. MPH normalised differences during sustained attention in fronto-striatal and fronto-cerebellar connectivity.
Vloet et al. (in press)	fMRI, PPI	Combined interference and time discrimination task	$N = 14$ children with ADHD compared to 14 controls (aged 8–15 years)	Functional connectivity analyses revealed abnormal fronto-parietal coupling during the interference task and reduced fronto-cerebellar connectivity during the Time discrimination task in the ADHD group compared to controls.

TABLE I. (Continued)

Authors	Measures	Task	Subjects	Findings
		DTI studies		
Ashtari et al. (2005)	DTI, FA		$N = 18$ children with ADHD compared to $N = 15$ controls	Decreased FA in right premotor, right striatal, right cerebral peduncle, left middle cerebellar peduncle, left cerebellum, and left parieto-occipital areas
Makris et al (2008)	DTI, FA	CB and SLF II	$N = 12$ adults with childhood ADHD compared to $N = 17$ controls	Significantly lower FA values in both regions of interest in the right hemisphere, in contrast to a control region (the fornix) in ADHD compared to control subjects
Casey et al. (2007)	DTI, FA	Automated fiber-tracking algorithm was used to delineate white matter fibers adjacent to functionally defined regions as identified by a Go-Nogo task	$N = 20$ parent–child dyads with ADHD and $N = 10$ dyads without ADHD	FA in right prefrontal fiber tracts correlated with both functional activity in the inferior frontal gyrus and caudate nucleus and performance of a go/nogo task in parent-child dyads with ADHD, even after controlling for age. Prefrontal fiber tract measures were tightly associated between ADHD parents and their children.
Pavuluri et al. (2009)	DTI, FA, ADC, r-FCI	Eight fiber tracts: ACR, ALIC, SRI, PLIC, SLF, ILF, CG, SP.	$N = 13$ PBD, $N = 13$ ADHD compared to $N = 15$ controls	Significantly lower FA was observed in ACR in both PBD and ADHD relative to HC. In addition, FA and r-FCI values were significantly lower in ADHD relative to PBD and HC in both the ALIC and the SRI. Further, ADC was significantly greater in ADHD relative to both the PBD and HC in ACR, ALIC, PLIC, SRI, CG, ILF, and SLF.
Hamilton et al. (2008)	DTI, FA within the cingulum, corpus callosum, corticospinal tract, fornix, optic radiations, superior longitudinal fasciculus, uncinate fasciculus, and the superior and inferior occipitofrontal fasciculi		$N = 17$ children and adolescents with ADHD compared to $N = 16$ age-matched controls	ADHD patients had significantly lower FA in the corticospinal tract and the superior longitudinal fasciculus compared to controls.
Silk et al. (2009)	DTI, FA and mean diffusity in ROIs of the basal ganglia		$N = 15$ male children and adolescents with ADHD compared to $N = 15$ age-matched controls (aged 8–18 years)	In the caudate nucleus, developmental changes in FA with age were significantly different between subjects with ADHD and controls.

ROI, region of interest; LFF, low-frequency fluctuations; dACC, dorsal anterior cingulate cortex; DMN, default-mode network; ReHO, regional homogeneity; SVM, support vector machine; ALFF, amplitude of low-frequency fluctuation; RSAI, resting state activity index; DC-EEG, direct current electroencephalogram; VLFO, very low frequency oscillations; ICA, independent component analysis; VLPFC, ventrolateral prefrontal cortex; MPH, methylphenidate; PPI, psychophysiological interaction; DTI, diffusion tensor imaging; FA, fractional anisotropy; CB, cingulum bundle; SLF II, superior longitudinal fasciculi; ADC, apparent diffusion coefficient; r-FCI, regional fiber coherence index; ACR, anterior corona radiata; ALIC, anterior limb of the internal capsule; SRI, superior region of the internal capsule; PLIC, posterior limb of the internal capsule; SLF, superior longitudinal fasciculus; ILF, inferior longitudinal fasciculus; CG, cingulum; SP, splenium; PBD, pediatric bipolar disorder; HC, healthy controls.

(such as choice of seed ROIs, considerations of anticorrelations, etc.) or might result from artifacts generated by the use of typically small samples; further, it is in line with currently held concepts of large heterogeneity among ADHD subjects. It is also possible that the heterogeneity of DMN findings simply mirrors the cognitive/"energetic"

variability that is often claimed to be one of the fundamental cognitive dysfunctions in ADHD.

Evidence for deviant connectivity patterns revealed during cognitive tasks in ADHD

Only a very limited number of studies have investigated the functional interactions of different brain regions during cognitive tasks in subjects with ADHD (Table I). One of the first studies to examine adults with ADHD found evidence for lower connectivity between the bilateral VLPFC, the anterior cingulate cortex, the superior parietal lobule and the cerebellum during a working memory task in these patients compared to healthy controls. In contrast, increased functional connectivity between the right prefrontal cortex, the left dorsal cingulate cortex and the left cuneus was found in ADHD adults. Two other studies investigating children and adolescents with ADHD found evidence for reduced fronto-striato-parieto-cerebellar connectivity but not for a compensatory increase in functional connectivity. For example, Rubia et al. [2009] reported decreased functional connectivity in the fronto-striato-parieto-cerebellar vigilance network in children with ADHD compared to controls. Interestingly, this decreased connectivity was normalized by methylphenidate except for a persistent deficit in parieto-cerebellar functional connectivity. Vloet et al. [in press], by analyzing psychophysiological interaction (PPI), also demonstrated reduced fronto-parietal and fronto-cerebellar connectivity in ADHD during a combined interference and time discrimination task.

Several studies have investigated how psychostimulants, the treatment of choice in subjects with ADHD, modulate neural activity during a variety of cognitive tasks. In contrast, very little is known about the modulating effects of methylphenidate (MPH) on the patterns of functional or effective connectivity within neural networks. Recently, Rubia et al. [2009] showed that MPH normalized the initially reduced fronto-striatal and fronto-cerebellar connectivity during sustained attention in patients with ADHD. The authors pointed out that the effect of MPH on functional connectivity was more prominent than its modulation of regionally specific activation strength, pointing to a predominant network dysfunction in ADHD. Peterson et al. [2009] reported that psychostimulants in adolescents with ADHD improved suppression of default-mode activity in the ventral anterior cingulate and posterior cingulate cortices during the commencement of structured cognitive tasks. It therefore appears that these drugs may improve symptoms related to ADHD by normalizing activity within a circuit related to the DMN and improving its functional interactions with the lateral prefrontal cortex.

On integrating the findings from subjects with ADHD into a developmental framework, the idea emerges that connectivity patterns in ADHD subjects resemble, at least in part, the connectivity patterns observed in younger typically developing subjects, e.g., with respect to reduced fronto-parietal connectivity during tasks that require working memory and interference suppression (Edin et al., 2007; Neufang et al., 2008]. No study design to date, however, has directly tested the hypothesis of delayed brain maturation with respect to functional connectivity patterns (see also Shaw et al. in this issue). One could speculate that increases in functional connectivity, which have been observed only in adults with ADHD, might represent compensatory processes that are established during the lifespan in response to reduced neural network efficiencies.

Abnormal structural connectivity in ADHD as shown by DTI studies

Thus far, studies investigating white matter development and anatomical connectivity in subjects with ADHD have yielded inconsistent findings. Whereas studies in children and adolescents with ADHD have shown a reduction in overall WM volume compared to normal controls [Castellanos et al., 2002], a trend toward an overall increase in WM volume in adults with ADHD has been demonstrated [Seidman et al., 2006]. The specificity of both studies, however, is compromised by the fact that both considered the entire cerebral WM volume without investigating specific fiber pathways or linking their findings to functional brain networks. Because DTI is still an emerging technique, only a limited number of DTI studies to date have investigated differences in anatomical connectivity between children with ADHD and healthy controls (Table I). Ashtari et al. [2005] reported that children with ADHD had decreased FA in the white matter underlying the premotor and left parieto-occipital cortices, as well as in the cerebellum and near the striatum. Casey et al. [2007] used fMRI maps from a go/no-go task to identify portions of the VLPFC and striatum involved in suppressing an inappropriate action in parent–child dyads with and without ADHD. They reported FA in the right prefrontal fiber tracts to be correlated with functional activity in the inferior frontal gyrus and caudate nucleus, as well as with behavioral task performance, in ADHD. Furthermore, prefrontal fiber tract measures were correlated between ADHD parents and their children, suggesting a genetic basis for the disturbance of fronto-striatal connections in ADHD. Makris et al. [2008] demonstrated abnormalities of the cingulum bundle and superior longitudinal fascicle (SLF) II (the major component of SLF, which originates in the caudal-inferior parietal cortex, terminates in the dorsolateral prefrontal cortex and is involved in attention and executive functions) in adults with ADHD. The finding of lower FA in the corticospinal tract and the SFL [Hamilton et al., 2008] similarly suggested disruption of motor and attention networks in children with ADHD. Finally, decreased FA in the anterior corona radiata and abnormalities across multiple white matter tracts, including the cingulum bundle, the superior and inferior longitudinal fasciculi and the internal capsule were reported in ADHD patients by Pavuluri et al. [2009]. Interestingly, Silk et al. [2009] reported fronto-striatal and fronto-parietal circuit abnormalities in children with ADHD. Developmental changes in FA in the caudate

nucleus with age were significantly different between ADHD and control groups. The authors suggested that the difference in developmental trajectories might reflect a developmental delay in ADHD that begins to normalize over the course of adolescence.

Integration of findings from structural and functional connectivity studies suggests that the decreased global efficiency of brain networks observed in ADHD [Wang et al., 2009] might be associated with a loss of long-range connections. Preliminary DTI data indicate that brain regions that show ADHD-related functional abnormality, such as the anterior limb of the internal capsule (containing thalamocortical and corticopontine fibers) [Ashtari et al., 2005] or the corpus callosum [Hill et al., 2003; Semrud-Clikeman et al., 1994] are also associated with reduced FA. Thus, these structural abnormalities may negatively impact the long-range communication among parts of the brain. Wang et al. [2009] demonstrated abnormal nodal efficiency in several brain regions, including the prefrontal, temporal, occipital, and subcortical regions, during the resting state in subjects with ADHD. In particular, the finding of decreased nodal efficiency in the orbitofrontal cortex is in accord with the results of several structural and functional imaging studies that have found reduced neural activity, gray matter volume or myelination in this region in patients with ADHD [Lee et al., 2005; Makris et al., 2007]. Interestingly, while the inferior frontal gyrus (IFG) exhibited significantly increased nodal efficiency during resting state in ADHD [Wang et al., 2009], it showed reduced coupling with parietal and cerebellar brain regions during cognitive tasks of attention and response inhibition (Rubia et al., 2009; Vloet et al., in press]. Thus, one may speculate that the observation of greater nodal efficiency may reflect greater effort in the ADHD children, who cannot sufficiently compensate for the coupling deficit between the inferior frontal cortex and other brain regions during cognitive tasks.

While these findings suggest that both functional and structural networks are profoundly affected by ADHD, it remains to be elucidated how changes in anatomical connections are related to dysfunctional connectivity during rest and during tasks. In particular, the causality between disturbed white matter architecture and cortical dysfunction remains to be evaluated. Specifically, are pathologies of white matter development responsible for abnormal functional integration between cortical areas, or are they merely a reflection of disturbed regional brain function? While it remains to be seen whether these effects can be disentangled, the presence of abnormal anatomical and functional connectivity in ADHD clearly highlights the need to address this disorder from a systems perspective by assessing both regional dysfunction and dysfunctional connectivity.

CONCLUSIONS AND FUTURE DIRECTIONS

Multimodal analysis of structural and functional brain connectivity may provide the key to a better understanding of the network architecture that shapes and constrains cognitive and affective development. In addition, such findings will provide a much-needed framework for examining how fundamental aspects of large-scale organization are disrupted in neurodevelopmental disorders. Previous work suggests that combining a longitudinal approach with a systems perspective might also help to further our understanding of the developmental stages at which disruptions in neural networks emerge and manifest in ADHD. This approach can be expected to advance our knowledge of the mechanism behind the changes in the behavioral ADHD phenotype across the lifespan. For example, it has been suggested that smaller gray matter volumes in the caudate observed in children with ADHD show normalization during late adolescence [Castellanos et al., 2002], possibly reflecting the clinical observation that the hyperactivity of ADHD tends to diminish during this time. It is interesting to note that the caudate and putamen also show the largest changes in fractional anisotropy of white-matter tracts, increasing 30–50% between 5 and 25 years of age [Asato et al., in press]. Thus, the reduction of hyperactive symptoms during adolescence might be also associated with maturation of white-matter tracts between childhood and young adulthood.

To identify the stage of development at which disruptions in neural networks emerge and manifest, it is necessary to learn how genes and environmental factors impact neural network architecture. Many of the early neurodevelopmental processes that are believed to be disrupted in ADHD are likely to be mediated by genetic mechanisms. Genetic and environmental factors are also believed to be involved in the continuity of the disorder, as well as in changes in ADHD symptomatology, throughout life. It is well accepted that aspects of brain structure, organization and function are all under genetic influence (Koten et al., 2009; Lenroot et al., 2009]. With respect to disruption of connectivity patterns, it has been shown that healthy carriers of rs1344706 risk genotypes that are associated with schizophrenia do not exhibit changes in regional brain activity, but pronounced gene dosage-dependent alterations in functional coupling (correlated activity) of DLPFC occur across hemispheres and with the hippocampus, mirroring findings in patients. These data suggest that altered connectivity may soon emerge as part of a core neurogenetic architecture of psychiatric disorders. It is generally accepted that the effects of variations in any single gene are not likely to be highly influential in the disease process. Rather, genetic influences in ADHD and in other psychiatric illnesses do not directly alter the phenotype in a simple Mendelian manner but are complex (i.e., multigenetic) in nature, such that a large network of small genetic variations may add and interact to produce the disruption of neural architecture that is behaviorally expressed as ADHD. The exact mechanisms through which these factors affect neural development and connectivity are still under investigation. Some of these genes may not be broadly involved in the neurodevelopmental process but may instead interact with specific neural pathways involved in symptom presentation and functional deficits. Other potential risk genes for ADHD, such as

neurotrophic factors (NTFs; Ribasés et al., 2008], which affect neuronal survival and synaptic efficiency, might exert a myriad of effects on the processes of neuronal migration, myelination and neuronal integrity and are thus strong candidates to contribute to the neuroplastic changes that take place in the human central nervous system during childhood, adolescence, and early adulthood. For example, BDNF and nerve growth factor (NGF), both of which are members of the neurotrophin family and are involved in the survival, differentiation, and maintenance of neuronal cells, have already been tentatively linked with ADHD [Kent et al. 2005; Syed et al. 2007].

Some of the developmental disruptions observed in patients with ADHD also appear to be influenced by environmental rather than genetic factors. Among the most consistently reported environmental risk factors affecting early developmental processes in ADHD are low birth weight [Mick et al., 2002] and perinatal exposure to teratogens [Rodriguez and Bohlin, 2005]. Interestingly, recent DTI studies demonstrated that differences in FA between adolescents born prematurely with very low birth weight and controls could be also identified in several WM areas that are similar to those brain areas reported in subjects with ADHD. Low FA values in specific areas were associated with perceptual, cognitive and motor impairments in prematurely born adolescents [Skranes et al., 2007]. These data indicate that, in addition to certain genetic effects, other neurobiological risk factors might result in similar deviant patterns of WM development and may be associated with persisting symptoms of ADHD.

Moving toward a neural systems concept of ADHD and aiming for a better understanding of how cortical networks and their development are specifically altered in one patient group compared to another by cross-syndrome comparisons may provide new avenues to understanding developmental disorders in future studies. Characterization of these neural systems may further allow the identification of new endophenotypes of dysfunction that can be used for in vivo categorization and may help to correlate these endophenotypes with genes on the one hand and behaviors on the other. In addition, findings of abnormal structural and functional connectivity in ADHD should be viewed from a refined developmental perspective, requiring more longitudinal structural and functional imaging studies to be performed. In particular, study designs that permit testing of the hypothesis of delayed versus altered maturation of neural networks is promising. As the methodologies for measuring structural and functional connectivity continue to improve and if their complementary strengths are applied in parallel, we can expect important advances in our diagnostic and prognostic capacities in developmental disorders such as ADHD.

REFERENCES

Arnold SE, Rioux L (2001): Challenges, status, and opportunities for studying developmental neuropathology in adult schizophrenia. Schizophr Bull 27:395–416.

Ashtari M, Kumra S, Bhaskar SL, Clarke T, Thaden E, Cervellione KL, Rhinewine J, Kane JM, Adesman A, Milanaik R, Maytal J, Diamond A, Szeszko P, Ardekani BA (2005): Attention-deficit/hyperactivity disorder: A preliminary diffusion tensor imaging study. Biol Psychiatry 57:448–455.

Asato MR, Terwilliger R, Woo J, Luna B: White matter development in adolescence: A DTI study. Cereb Cortex 2010 Jan 5. [Epub ahead of print].

Beckmann CF, DeLuca M, Devlin JT, Smith SM (2005): Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc Lond B 360.

Biederman J, Faraone SV (2006): The effects of attention-deficit/hyperactivity disorder on employment and household income. Med Gen Med 8:12.

Birn RM, Murphy K, Bandettini PA (2008): The effect of respiration variations on independent component analysis results of resting state functional connectivity. Hum Brain Mapp 29:740–750.

Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJ (2009): Default-mode brain dysfunction in mental disorders: A systematic review. Neurosci Biobehav Rev 33:279–296.

Buzsáki G, Draguhn A (2004): Neuronal oscillations in cortical networks. Science 304:1926–1929.

Casey BJ, Epstein JN, Buhle J, Liston C, Davidson MC, Tonev ST, Spicer J, Niogi S, Millner AJ, Reiss A, Garrett A, Hinshaw SP, Greenhill LL, Shafritz KM, Vitolo A, Kotler LA, Jarrett MA, Glover G (2007): Frontostriatal connectivity and its role in cognitive control in parent-child dyads with ADHD. Am J Psychiatry 164:1729–1736.

Cao Q, Zang Y, Sun L, Sui M, Long X, Zou Q, Wang Y (2006): Abnormal neural activity in children with attention deficit hyperactivity disorder: A resting-state functional magnetic resonance imaging study. Neuroreport 17:1033–1036.

Cao QJ, Zang YF, Wang YF (2007): Brain functions in attention deficit hyperactivity disorder combined and inattentive subtypes: A resting-state functional magnetic resonance imaging study. Beijing Da Xue Xue Bao 39:261–265.

Cao X, Cao Q, Long X, Sun L, Sui M, Zhu C, Zuo X, Zang Y, Wang Y (2009): Abnormal resting-state functional connectivity patterns of the putamen in medication-naïve children with attention deficit hyperactivity disorder. Brain Res. 1303:195–206.

Castellanos FX, Margulies DS, Kelly C, Uddin LQ, Ghaffari M, Kirsch A, Shaw D, Shehzad Z, Di Martino A, Biswal B, Sonuga-Barke EJ, Rotrosen J, Adler LA, Milham MP (2008): Cingulate-precuneus interactions: A new locus of dysfunction in adult attention-deficit/hyperactivity disorder. Biol Psychiatry 63:332–337.

Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, Blumenthal JD, James RS, Ebens CL, Walter JM, Zijdenbos A, Evans AC, Giedd JN, Rapoport JL (2002): Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. JAMA 288:1740–1748.

Damoiseaux JS, Greicius MD (2009): Greater than the sum of its parts: A review of studies combining structural connectivity and resting-state functional connectivity. Brain Struct Funct 213:525–533.

Doyle AE, Willcutt EG, Seidman LJ, Biederman J, Chouinard VA, Silva J, Faraone SV (2005): Attention-deficit/hyperactivity disorder endophenotypes. Biol Psychiatry 57:1324–1335.

Edin F, Klingberg T, Stödberg T, Tegnér J (2007): Fronto-parietal connection asymmetry regulates working memory distractibility. J Integr Neurosci 6:567–596.

Eichele T, Debener S, Calhoun VD, Specht K, Engel AK, Hugdahl K, von Cramon DY, Ullsperger M (2008): Prediction of human errors by maladaptive changes in event-related brain networks. Proc Natl Acad Sci USA 105:6173–6178.

Eickhoff SB, Laird AR, Grefkes C, Wang LE, Zilles K, Fox PT (2009a): Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: A random-effects approach based on empirical estimates of spatial uncertainty. Hum Brain Mapp 30:2907–2926.

Eickhoff SB, Heim S, Zilles K, Amunts K (2009b): A systems perspective on the effective connectivity of overt speech production. Philos Transact A Math Phys Eng Sci 367:2399–2421.

Eickhoff SB, Dafotakis M, Grefkes C, Stöcker T, Shah NJ, Schnitzler A, Zilles K, Siebler M (2008): fMRI reveals cognitive and emotional processing in a long-term comatose patient. Exp Neurol 214:240–246.

Fair DA, Cohen AL, Dosenbach NU, Church JA, Miezin FM, Barch DM, Raichle ME, Petersen SE, Schlaggar BL (2008): The maturing architecture of the brain's default network. Proc Natl Acad Sci USA 105:4028–4032.

Fair DA, Dosenbach NU, Church JA, Cohen AL, Brahmbhatt S, Miezin FM, Barch DM, Raichle ME, Petersen SE, Schlaggar BL (2007): Development of distinct control networks through segregation and integration. Proc Natl Acad Sci USA 104:13507–13512.

Fox MD, Raichle ME (2007): Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 8:700–711.

Fox MD, Snyder AZ, Zacks JM, Raichle ME (2006): Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses. Nat Neurosci 9:23–25.

Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005): The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci USA 102:9673–9678.

Friston K (2002): Functional integration and inference in the brain. Prog Neurobiol 68:113–143.

Grefkes C, Eickhoff SB, Nowak DA, Dafotakis M, Fink GR (2008): Dynamic intra- and interhemispheric interactions during unilateral and bilateral hand movements assessed with fMRI and DCM. Neuroimage 41:1382–1394.

Greicius MD, Kiviniemi V, Tervonen O, Vainionpää V, Alahuhta S, Reiss AL, Menon V (2008): Persistent default-mode network connectivity during light sedation. Hum Brain Mapp 29:839–847.

Greicius MD, Menon V (2004): Default-mode activity during a passive sensory task: Uncoupled from deactivation but impacting activation. J Cogn Neurosci 16:1484–1492.

Hamilton LS, Levitt JG, O'Neill J, Alger JR, Luders E, Phillips OR, Caplan R, Toga AW, McCracken J, Narr KL (2008): Reduced white matter integrity in attention-deficit hyperactivity disorder. Neuroreport 19:1705–1708.

Helps S, James C, Debener S, Karl A, Sonuga-Barke EJ (2008): Very low frequency EEG oscillations and the resting brain in young adults: A preliminary study of localisation, stability and association with symptoms of inattention. J Neural Transm 115:279–285.

Honey CJ, Kötter R, Breakspear M, Sporns O (2007): Network structure of cerebral cortex shapes functional connectivity on multiple time scales. Proc Natl Acad Sci USA 104:10240–10245

Kent L, Green E, Hawi Z, Kirley A, Dudbridge F, Lowe N, Raybould R, Langley K, Bray N, Fitzgerald M, et al. (2005): Association of the paternally transmitted copy of common Valine allele of the Val66Met polymorphism of the brain-derived neurotrophic factor (BDNF) gene with susceptibility to ADHD. Mol Psychiatry 10:939–943.

Koten JW Jr, Wood G, Hagoort P, Goebel R, Propping P, Willmes K, Boomsma DI (2009): Genetic contribution to variation in cognitive function: an FMRI study in twins. Science 323:1737–1740.

Laird AR, Eickhoff SB, Kurth F, Fox PM, Uecker AM, Turner JA, Robinson JL, Lancaster JL, Fox PT (2009): ALE Meta-analysis workflows via the brainmap database: Progress towards a probabilistic functional brain atlas. Front Neuroinformatics 3:23.

Laird AR, Eickhoff SB, Li K, Robin DA, Glahn DC, Fox PT (2009): Investigating the functional heterogeneity of the default mode network using coordinate-based meta-analytic modeling. J Neurosci 29:14496–14505.

Le Bihan D (2003): Looking into the functional architecture of the brain with diffusion MRI. Nat Rev Neurosci 4:469–480.

Lenroot RK, Schmitt JE, Ordaz SJ, Wallace GL, Neale MC, Lerch JP, Kendler KS, Evans AC, Giedd JN (2009): Differences in genetic and environmental influences on the human cerebral cortex associated with development during childhood and adolescence. Hum Brain Mapp 30:163–174.

Li CS, Yan P, Bergquist KL, Sinha R (2007): Greater activation of the "default" brain regions predicts stop signal errors. Neuroimage 38:640–648.

Makris N, Buka SL, Biederman J, Papadimitriou GM, Hodge SM, Valera EM, Brown AB, Bush G, Monuteaux MC, Caviness VS, Kennedy DN, Seidman LJ (2008): Attention and executive systems abnormalities in adults with childhood ADHD: A DT-MRI study of connections. Cereb Cortex 18:1210–1220.

Mick E, Biederman J, Prince J, Fischer MJ, Faraone SV (2002): Impact of low birth weight on attention-deficit hyperactivity disorder. J Dev Behav Pediatr 23:16–22.

Moseley ME, Cohen Y, Kucharczyk J, Mintorovitch J, Asgari HS, Wendland MF, Tsuruda J, Norman D (1990): Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system. Radiology 176:439–445.

Murphy K, Birn RM, Handwerker DA, Jones TB, Bandettini PA (2009): The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? Neuroimage 44:893–905.

Neufang S, Fink GR, Herpertz-Dahlmann B, Willmes K, Konrad K (2008): Developmental changes in neural activation and psychophysiological interaction patterns of brain regions associated with interference control and time perception. Neuroimage 43:399–409.

Paus T, Collins DL, Evans AC, Leonard G, Pike B, Zijdenbos A (2001): Maturation of white matter in the human brain: a review of magnetic resonance studies. Brain Res Bull 54:255–266.

Pavuluri MN, Yang S, Kamineni K, Passarotti AM, Srinivasan G, Harral EM, Sweeney JA, Zhou XJ (2009): Diffusion tensor imaging study of white matter fiber tracts in pediatric bipolar disorder and attention-deficit/hyperactivity disorder. Biol Psychiatry 65:586–593.

Peterson BS, Potenza MN, Wang Z, Zhu H, Martin A, Marsh R, Plessen KJ, Yu S (2009): An fMRI study of the effects of psychostimulants on default-mode processing during stroop task performance in youths With ADHD. Am J Psychiatry 166:1286–1294.

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001): A default mode of brain function. Proc Natl Acad Sci USA 98:676–682.

Ribasés M, Hervás A, Ramos-Quiroga JA, Bosch R, Bielsa A, Gastaminza X, Fernández-Anguiano M, Nogueira M, Gómez-Barros N, Valero S, Gratacòs M, Estivill X, Casas M, Cormand B, Bayés M (2008): Association study of 10 genes encoding neurotrophic factors and their receptors in adult and child attention-deficit/hyperactivity disorder. Biol Psychiatry 63:935–945.

Rodriguez A, Bohlin G (2005): Are maternal smoking and stress during pregnancy related to ADHD symptoms in children? J Child Psychol Psychiatry 46:246–254.

Rubia K, Cubillo A, Smith AB, Woolley J, Heyman I, Brammer MJ (2009): Disorder-specific dysfunction in right inferior prefrontal cortex during two inhibition tasks in boys with attention-deficit hyperactivity disorder compared to boys with obsessive-compulsive disorder. Hum Brain Mapp 31:287–299.

Schilbach L, Eickhoff SB, Rotarska-Jagiela A, Fink GR, Vogeley K (2008): Minds at rest? Social cognition as the default mode of cognizing and its putative relationship to the "default system" of the brain. Conscious Cogn 17:457–467.

Sergeant JA, Geurts H, Huijbregts S, Scheres A, Oosterlaan J (2006): The top and the bottom of ADHD: A neuropsychological perspective. Neurosci Biobehav Rev 27:583–592.

Seidman LJ, Valera EM, Makris N, Monuteaux MC, Boriel DL, Kelkar K, Kennedy DN, Caviness VS, Bush G, Aleardi M, Faraone SV, Biederman J (2006): Dorsolateral prefrontal and anterior cingulate cortex volumetric abnormalities in adults with attention-deficit/hyperactivity disorder identified by magnetic resonance imaging. Biol Psychiatry 60:1071–1080.

Shaw P, Gogtay N, Rapoport J (2010): Childhood psychiatric disorders as anomalies in neurodevelopmental trajectories. Human Brain Mapping.

Silk TJ, Vance A, Rinehart N, Bradshaw JL, Cunnington R (2009): White-matter abnormalities in attention deficit hyperactivity disorder: A diffusion tensor imaging study. Hum Brain Mapp 30:2757–2765.

Singh KD, Fawcett IP (2008): Transient and linearly graded deactivation of the human default-mode network by a visual detection task. Neuroimage 41:100–112.

Skranes J, Vangberg TR, Kulseng S, Indredavik MS, Evensen KA, Martinussen M, Dale AM, Haraldseth O, Brubakk AM (2007): Clinical findings and white matter abnormalities seen on diffusion tensor imaging in adolescents with very low birth weight. Brain 130:654–666.

Sonuga-Barke EJ, Castellanos FX (2007): Spontaneous attentional fluctuations in impaired states and pathological conditions: a neurobiological hypothesis. Neurosci Biobehav Rev 1:977–986.

Supekar K, Musen M, Menon V (2009). Development of large-scale functional brain networks in children. PLoS Biol 7: e1000157.

Syed Z, Dudbridge F, Kent L (2007): An investigation of the neurotrophic factor genes GDNF, NGF and NT3 in susceptibility to ADHD. Am J Med Genet Part B: Neuropsychiatric Genet 144:375–378.

Tian L, Jiang T, Liang M, Zang Y, He Y, Sui M, Wang Y (2008): Enhanced resting-state brain activities in ADHD patients: A fMRI study. Brain Dev 30:342–348.

Tian L, Jiang T, Wang Y, Zang Y, He Y, Liang M, Sui M, Cao Q, Hu S, Peng M, Zhuo Y (2006): Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder. Neurosci Lett 400:39–43.

Tzourio-Mazoyer N, De Schonen S, Crivello F, Reutter B, Aujard Y, Mazoyer B (2002): Neural correlates of woman face processing by 2-month-old infants. Neuroimage 15:454–461.

Uddin LQ, Kelly AM, Biswal BB, Margulies DS, Shehzad Z, Shaw D, Ghaffari M, Rotrosen J, Adler LA, Castellanos FX, Milham MP (2008): Network homogeneity reveals decreased integrity of default-mode network in ADHD. J Neurosci Methods 169:249–254.

Vloet TD, Gilsbach S, Neufang S, Fink GR, Herpertz-Dahlmann B, Konrad K (2010): Neural mechanisms of interference control and time discrimination in attention-deficit/hyperactivity disorder. JAACAP 49:356–367.

Wang L, Zhu C, He Y, Zang Y, Cao Q, Zhang H, Zhong Q, Wang Y (2009): Altered small-world brain functional networks in children with attention-deficit/hyperactivity disorder. Hum Brain Mapp 30:638–649.

Watts DJ, Strogatz SH (1998): Collective dynamics of 'small-world' networks. Nature 393:409–410.

Weissman DH, Roberts KC, Visscher KM, Woldorff MG (2006): The neural bases of momentary lapses in attention. Nat Neurosci 9:971–978.

Wolf RC, Plichta MM, Sambataro F, Fallgatter AJ, Jacob C, Lesch KP, Herrmann MJ, Schönfeldt-Lecuona C, Connemann BJ, Grön G, Vasic N (2009): Regional brain activation changes and abnormal functional connectivity of the ventrolateral prefrontal cortex during working memory processing in adults with attention-deficit/hyperactivity disorder. Hum Brain Mapp 30:2252–2266.

Zang YF, He Y, Zhu CZ, Cao QJ, Sui MQ, Liang M, Tian LX, Jiang TZ, Wang YF (2007): Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. Brain Dev 29:83–91.

Zhu CZ, Zang YF, Cao QJ, Yan CG, He Y, Jiang TZ, Sui MQ, Wang YF (2008): Fisher discriminative analysis of resting-state brain function for attention-deficit/hyperactivity disorder. Neuroimage 40:110–120.

Zhu CZ, Zang YF, Liang M, Tian LX, He Y, Li XB, Sui MQ, Wang YF, Jiang TZ (2005): Discriminative analysis of brain function at resting-state for attention-deficit/hyperactivity disorder. Med Image Comput Comput Assist Interv Int Conf Med Image Comput Comput Assist Interv 8:468–475.