



Review

Imaging genetics in ADHD: A focus on cognitive control

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ABSTRACT

This paper evaluates neuroimaging of cognitive control as an endophenotype for investigating the role of dopamine genes in ADHD. First, this paper reviews both data-driven and theory-driven approaches from genetics and neuroimaging. Several viable candidate genes have been implicated in ADHD, including the dopamine DRD4 and DAT1 genes. Neuroimaging studies have resulted in a good understanding of the neurobiological basis of deficits in cognitive control in this disorder. Second, this paper discusses imaging genetics in ADHD. Papers to date have taken one of two approaches: whereas early papers investigated the effects of one or two candidate genes on many brain areas, later papers constrained regions of interest by gene expression patterns. These papers have largely focused on cognitive control and the dopamine circuits involved in this ability. The results show that neuroimaging of cognitive control is useful as an endophenotype in investigating dopamine gene effects in ADHD. Other avenues of investigation are suggested by a combination of data- and theory-driven approaches in both genetics and neuroimaging.

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Contents

1. Introduction	674
2. Methods	675
3. Heritability and genes in ADHD	676
3.1. Whole genome linkage studies	676
3.2. Candidate gene studies	676
3.3. Gene expression	677
4. Imaging of brain structure and function in ADHD	678
4.1. Imaging brain function	678
4.2. Imaging brain structure	681
5. Imaging heritability and genes in ADHD	682
5.1. Imaging genetics of cognitive control in ADHD	683
5.2. Other leads in imaging genetics in ADHD: the cerebellum	684
5.3. Other leads in imaging genetics in ADHD: the serotonin transporter gene	685
6. Conclusion	685
7. Beyond studying the biology of ADHD	685
References	685

1. Introduction

This special issue of *Neuroscience and Biobehavioral Reviews* is dedicated to control of action and cognition. This type of control is of longstanding interest to investigators interested in attention deficit/hyperactivity disorder (ADHD), as it is often compromised in individuals with this disorder. In ADHD research, this ability is often referred to as cognitive control and is defined as the ability to suppress inappropriate behaviors in favor of appropriate ones,

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leading to the ability to flexibly adapt behavior in the face of changing circumstances. Its relevance to ADHD is reflected by the diagnostic criteria for the disorder, which include descriptions of ‘not being able to sit still in class’ and ‘blurting out answers to questions before they have been completed’ (suppressing inappropriate behavior), as well as ‘having difficulty organizing tasks and activities’ and ‘losing things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)’ (adapting behavior as required by circumstances) (APA, 2000). Problems in cognitive control have even been suggested to be central to this disorder (Barkley, 1997), although this simple explanation cannot explain all the phenotypic variance in ADHD, as only 30–50% of children with ADHD have significantly impaired performance on tests of this ability (Casey and Durston, 2006; Nigg et al., 2005).

This paper aims to evaluate neuroimaging measures of cognitive control as an endophenotype for investigating the neurobiology of ADHD, and specifically for investigating the role of dopamine genes in this disorder. The brain circuitry underlying cognitive control is widely investigated and, as a result, is relatively well understood (see Chambers et al., this issue for a comprehensive discussion). Catecholamine systems are central to cognitive control: small variations in noradrenaline or dopamine levels in prefrontal cortex have profound effects on cognitive functioning in animal models (Arnsten and Li, 2005; Castner et al., 2005). Furthermore, these neurotransmitter systems have been implicated in ADHD in a wide variety of studies. To name but one example: DAT1 knock-out mice shown hyperactivity in novel surroundings that can be improved using stimulant medication that works on catecholamine systems. Interestingly, this effect appears to be mediated by serotonin systems, illustrating the subtle nature of monoamine interactions that are involved in fine-tuning behavior (Gainetdinov et al., 1999).

Endophenotypes are intermediate between a behavioral classification (such as ADHD) and the biological variables that are the cause of the disorder (whether genetic or environmental). Using such intermediate phenotypes can be advantageous in studying psychiatric disorders, such as ADHD, as they have the potential to overcome some of the limitations of approaches using diagnostic categories as end-points: the use of diagnostic categories may create heterogeneous groups, as subjects are included based on a behavioral phenotype that may reflect an array of biological causes. This is obviously problematic in investigations of the neurobiology of such disorders, including both genetic association and fMRI studies (see Castellanos and Tannock, 2002; Gottesman and Gould, 2003). A particular strength of the endophenotype approach is that it aims to identify neurobiological markers within more homogeneous subgroups and, as such, is less susceptible to the noise inherent to heterogeneity. A number of theorists have outlined criteria that endophenotypes should meet in order to be beneficial the study of causative agents in psychiatry. These are summarized in

Table 1

Criteria for endophenotypes for investigating gene effects in psychiatry (adapted from Almay and Blangero, 2001; Castellanos and Tannock, 2002; Gottesman and Gould, 2003)

Criteria for intermediate phenotypes in psychiatric research
(1) Continuously quantifiable
(2) Stable (a trait as opposed to a state measure)
(3) Closer to the causative agent (e.g., genes and gene expression) than the disorder
(4) Associated with disorder
(5) Probabilistically predictive of the disorder
(6) Cluster in families where the disorder is found
(7) Found in unaffected relatives of affected individuals
(8) Grounded in neuroscience

Table 1. Endophenotype approaches by their nature require a theoretical approach to a disorder, as a phenotype associated with it is linked to a biological pathway. This is not necessarily true of genetics or neuroimaging, where whole-genome or whole-brain analyses can be conducted in a data-driven manner. In this paper, we first review the genetic and neuroimaging literature on ADHD. We discuss data-driven and theory-driven approaches from both. Next, we review the literature using neuroimaging measures as endophenotypes in ADHD and assess the value of cognitive control as such a measure.

2. Methods

Genetic and MRI original research papers were retrieved through Pubmed and ISI Web of Science. Search terms were ‘Attention deficit and hyperactivity disorder’, ‘ADHD’ and ‘association study’, ‘genetic study’, ‘heritability’, ‘linkage study’, ‘genome wide study’, ‘genome wide scan’ or ‘genetic risk’ for genetic studies. ‘ADHD’, ‘MRI’ and ‘fMRI’ were used for neuroimaging studies. Brain tissue expression and receptor localization for candidate genes were assessed by searches using the human UCSC Genome Browser, release March 2006 (Kent et al., 2002; <http://genome.ucsc.edu>) and the Allen Brain Atlas/Allen Institute for Brain Science (<http://www.brain-map.org>) and an additional Pubmed search. Papers were excluded if they contained *only* data described in earlier publication (i.e., reports of new analyses or subgroups of subjects were allowed). In the overview of whole-genome scans in Table 2, regions with LOD-score >2.0 were included, although scores >2.2 are typically considered suggestive of linkage (Albayrak et al., 2008; Lander and Kruglyak, 1995). We chose a slightly lower minimum score to minimize the chance of type II errors, where a suggestive replication is narrowly missed. For neuroimaging studies (Tables 5–7), only studies of subjects with a clinical ADHD diagnosis were included; studies of population-based samples were excluded. The naming of brain regions in Table 5 is based on the talairach co-ordinates reported and not on the nomenclature used in the original papers, as naming is not always consistent across studies and groups. In Tables 5 and 6, only results from the direct comparison of subjects with ADHD to controls are reported (i.e., findings within group, in comparison with other clinical samples and medication effects are not).

Table 2

Regions from whole-genome scans with maximum LOD score >2.0 associated with ADHD diagnosis

Region	Publication
2q35	Romanos et al. (2008)
5p13	Friedel et al. (2007), Hebebrand et al. (2006) and Ogdie et al. (2004)
5q13	Romanos et al. (2008)
5q33	Arcos-Burgos et al. (2004)
6q12	Fisher et al. (2002) and Ogdie et al. (2004)
6q22–23	Romanos et al. (2008)
7p13	Bakker et al. (2003)
7q21	Romanos et al. (2008)
9q22	Asherson et al. (2008) and Romanos et al. (2008)
9q33	Bakker et al. (2003)
11q22	Arcos-Burgos et al. (2004)
12p13	Fisher et al. (2002)
14q12	Romanos et al. (2008)
15q15	Bakker et al. (2003)
16q23	Asherson et al. (2008)
16q24	Romanos et al. (2008)
16p13	Ogdie et al. (2003, 2004)
17p11	Ogdie et al. (2003, 2004) and Arcos-Burgos et al. (2004)
No region	Faraone et al. (2007) and Fisher et al. (2002)

3. Heritability and genes in ADHD

ADHD is a common disorder with a significant heritable component. The disorder tends to cluster in families and additive genetic effects explaining up to 80% of the variance in the phenotype (e.g., Albayrak et al., 2008; Thapar et al., 1999). Concordance rates are estimated to lie between 50 and 80% for monozygotic twins and at around 30% dizygotic twins (Bradley and Golden, 2001; Thapar et al., 1999). Interestingly, although ADHD clusters in families, ADHD subtypes do not (Smalley et al., 2001). This suggests that there may not be a direct link between risk genes and the clinical phenotype, but rather that mediating factors may be involved.

The search for genes that convey risk for ADHD is ongoing. In a genome scan, all chromosomes are screened for linkage with markers spaced throughout the genome. When a region of interest is identified, it can be further explored using high-density mapping. This approach has the advantage that it does not require an a priori hypothesis of which genes (or regions on the genome) are involved. A disadvantage is that it cannot directly identify risk genes, as many genes lie under a single linkage peak and the linkage signal could be caused by any one of those. Candidate gene studies use a different approach, where a gene is selected on theoretical grounds. Its involvement in the disorder can then be investigated in a case-control or family-based design. Case-control designs have the disadvantage that they can be susceptible to population stratification effects, whereas family-based designs use transmission disequilibrium testing to test for preferential transmission of high-risk alleles to ADHD probands. This approach has been used in most candidate gene studies in ADHD to date.

3.1. Whole genome linkage studies

Table 2 shows regions implicated in whole genome linkage studies. Seventeen regions have been implicated in ten studies published to date, including data from four independent samples from Germany, the Netherlands, the USA and an isolated region of Colombia. Of those, only two regions have been implicated in more than one independent sample: 5p13 and 17p11. The region on 5p13 includes the DAT1 gene that has also been implicated in candidate gene studies (see Table 3). One group recently confirmed that their linkage peak on 5p13 (Hebebrand et al., 2006) was due to this gene by genotyping 30 single nucleotide polymorphisms (SNPs) within it and its 5' region (Friedel et al., 2007). They found that their linkage peak was related to genetic variation at the DAT1 locus. The serotonin transporter gene (5-HTT) lies on 17q11, relatively close to the peak on 17p11 in some analyses (Ogdie et al., 2004). It is notable that whole genome linkage studies include many more differences between studies than overlap. This suggests that ADHD is not related to a small number of genes of large effect, but is more likely caused by combinations of larger numbers of genes of small effect (Faraone et al., 2005).

3.2. Candidate gene studies

There have been many more studies investigating genes that are considered to be candidate risk genes for ADHD than genome wide explorations. Genes located in regions of suggestive or significant linkage have often been studied, as have genes in the catecholamine systems, given their theoretical relevance to the disorder (Arnsten, 2006; Casey and Durston, 2006; Durston, 2003; Durston, in press). These systems can be viewed as particularly relevant to ADHD, given the mechanisms of action for ADHD medication: methylphenidate (MPH) is thought to primarily exert its therapeutic effects by blocking the dopamine transporter (Volkow et al., 1998), although

Table 3
Candidate genes in ADHD research

Gene	Published negative associations	Published positive associations
Catecholamines		
COMT	7	1
Catecholamines: dopamine		
DAT1 (SLC6A3)	9	17
DRD1		2
DRD2	2	1
DRD3	1	
DRD4	10	21
DRD5	3	2
DBH	3	4
TH	1	
DARPP-32	1	
NR4A2		1
Catecholamines: norepinephrine		
NET1 (SLC6A2)	3	2
ADRA2A	1	5
ADRA2C	1	
ADRB2		1
PNMT		1
Other monoamines		
MAOA	3	5
MAOB	2	1
Other monoamines: serotonin		
5-HTT (SLC6A4)	5	4
5HTB1	1	2
5HTR2A	3	3
5HTR2B	1	
HTR4		1
TPH	1	1
TPH2	1	3
DDC	1	1
Other neurotransmitter systems: acetylcholine		
CHRNA4		1
CHRNA7	1	
Other genes		
SNAP25	1	4
BDNF	2	2
GDNF	2	
NGF	1	
NT3	1	
GRIN2A		1
FGF10	1	
ISL1	1	
HCN1	1	
ITGA1	1	
HLA-DRB1	1	
SLC1A3	1	1
CLOCK		1
ARRB2		1
SYP		1
HES1		1
FADS2		1
IL-1		1
AR		1
LIN-7		1

noradrenaline and serotonin systems may also be involved (Gainetdinov et al., 1999). A newer medication that is sometimes effective in ADHD is atomoxetine, a norepinephrine transporter blocker. Another monoamine system that has received attention is the serotonin system, given its implication in impulsive and hyperactive behavior (Oades, 2007).

Table 3 lists candidate genes that have been investigated in ADHD and the number of positive and negative associations reported for each gene. A table listing all references is available upon request from the authors. A total of 170 reports of the effects of

49 candidate genes have been published. There have been 96 reports of positive associations, including for 16 catecholamine genes, although many of these have failed to replicate in new samples. These studies are likely to have been hindered by the small effect of many ADHD risk genes, in line with observations of weak linkage signals. A further confound may be that most candidate gene studies have linked potential risk alleles to diagnosis, as opposed to a phenotype closer to the biology of a disorder. Diagnostic criteria reflect behavioral phenotypes and may therefore include multiple biological subtypes, with potentially different genetic underpinnings. The two genes that have been most frequently investigated are the dopamine DRD4 and DAT1 genes (see Table 3). Both positive and negative associations have been reported for both, with somewhat more positive reports. A fairly recent meta-analysis concluded that, to date, only seven candidate genes have risk alleles where the pooled odds ratio is significantly greater than 1.0, and that are therefore over-transmitted in ADHD. These genes include four catecholamine genes (the dopamine-4 and dopamine-5 receptors

(DRD4 and DRD5), dopamine transporter (DAT1), and dopamine-beta-hydroxylase (DBH)), two in the serotonin system (the serotonin transporter (5-HTT) and serotonin 1B-receptor (HTR1B) genes) and SNAP-25 (Faraone et al., 2005).

3.3. Gene expression

Gene expression in the brain is summarized in Table 4 for 13 of the most frequently replicated genes in ADHD. From this table, it is clear that many of these genes are expressed at a moderate level throughout the human brain. Expression appears to be somewhat more differentiated in the mouse brain. Furthermore, an additional Pubmed search suggested that there may be some differentiation in brain expression patterns, even in the human brain (last column). The best replicated candidate genes for ADHD, the DAT1 and DRD4 genes are expressed throughout the brain in humans, although protein localization and human gene expression studies suggest there may be relative over-expression in striatum (and

Table 4
Expression in the brain of genes associated with ADHD in at least two studies

Candidate gene (locus)	Expression in mouse	Expression in human	Additional expression or protein localization
Catecholamines: dopamine SLC6A3/DAT1 (5p15)	Midbrain	Whole brain moderate expression	Striatum (Garris and Wightman, 1994). Midbrain (Brookes et al., 2007; Giros et al., 1992; Shimada et al., 1992). Temporal lobe, cerebellum (Mill et al., 2002). Prefrontal cortex (Garris and Wightman, 1994). Amygdala (Garris and Wightman, 1994). Striatum (Augood et al., 2000; Hurd et al., 2001). Frontal cortex (Hurd et al., 2001)
DRD1 (5q35)	High expression in striatum, amygdala, olfactory areas, hippocampus	Whole brain high expression, particularly caudate nucleus and prefrontal cortex	
DRD4 (11p15)	Whole brain, enriched in ventral striatum, retro hippocampal region, olfactory areas, amygdala	Moderate expression in prefrontal, parietal and temporal lobes, cingulate cortex, cerebellum, basal ganglia	Prefrontal cortex (De La Garza and Madras, 2000; Noaín et al., 2006; Primus et al., 1997). Hippocampus (De La Garza and Madras, 2000; Primus et al., 1997). Hypothalamus, thalamus, entorhinal cortex, lateral septal nucleus (Mrzljak et al., 1996; Primus et al., 1997). Globus pallidus (Mrzljak et al., 1996)
DRD5 (4p16)	Whole brain high expression and receptor density	Whole brain moderate expression	Cerebellum, substantia nigra, hypothalamus, striatum, cerebral cortex, nucleus accumbens, hippocampus and olfactory tubercle (Beischlag et al., 1995; Khan et al., 2000)
DBH (9q34)	Medulla, pons	Whole brain moderate expression	Noradrenergic brain stem nuclei, sympathetic ganglion neurons (Hoyle et al., 1994) and hypothalamus, substantia nigra (Westlund et al., 1988)
Catecholamines: norepinephrine SLC6A2/NET1 (16q12)	Very low expression and receptor density in the brain	Whole brain moderate expression	Locus coeruleus (Eymin et al., 1995). Amygdala (Smith and Porrino, 2008)
ADRA2A (10q25)	Very low expression and receptor density in the brain	Moderate expression whole brain.	Cerebellum (Schambra et al., 2005)
Other monoamines MAOA (Xp11)	Moderate expression in pallidum	Moderate expression whole brain. High expression in thalamus, amygdala, occipital lobe and prefrontal cortex	Hypothalamus, nucleus coeruleus, substantia nigra (Westlund et al., 1988)
Serotonin SLC6A4, 5-HTT (17q11)	Limited expression and density in striatum and amygdala, pons, medulla, midbrain	Moderate whole brain expression	Midbrain, pons (Lim et al., 2006). Amygdala (O'Rourke and Fudge, 2006)
5HT1B (6q14)	High expression in striatum and cerebellum	Moderate expression in whole brain. High expression in prefrontal cortex and amygdala	NI raphe (Bidmon et al., 2001). Substantia nigra, globus pallidus, striatum, amygdala, hippocampus, and the cerebral cortex (Varnäs et al., 2001)
5HTR2A (13q14)	Very low expression and receptor density in the brain	High expression in the whole brain, particularly the prefrontal cortex	Prefrontal cortex (De Almeida and Mengod, 2007; Hall et al., 2000)
TPH2 (12q21)	Very low expression and receptor density in the brain	Whole brain moderate expression. High expression in cingulate cortex and globus pallidus	Raphe nuclei (Zill et al., 2007). Pons (Lim et al., 2007)
Other SNAP25 (20p11.2)	Whole brain high expression and receptor density	Whole brain high expression	Whole brain high expression (Garbelli et al., 2008)

The frontal lobes include prefrontal and orbitofrontal cortex. The basal ganglia include putamen, caudate nucleus, nucleus accumbens, globus pallidus, subthalamic nucleus and substantia nigra. The diencephalon includes thalamus, hypothalamus, subthalamus and pretectum. The Midbrain includes internal structures such as the raphe nuclei, the red nucleus and the reticular formation (including the locus coeruleus).

midbrain) and prefrontal cortex, respectively. For the 5-HTT gene (which has been suggestively implicated by whole genome approaches and candidate gene studies), there is a suggestion of over-expression in the medial temporal lobe structures, the amygdala in particular.

Not all changes in DNA structure of putative risk genes for ADHD necessarily have functional consequences. Theoretically, effects of a risk allele can only be relevant if they are associated with changes in expression of the gene in vivo. The 5-HTT gene is a good example of a gene where the risk allele has been shown to have functional consequences, as the short allele of the promoter polymorphism is associated with reduced expression of the gene and lessened availability of the transporter (Lesch et al., 1996). Furthermore, we know from fMRI studies that this polymorphism influences amygdala activity (Hariri et al., 2002). This is a major advantage as these data can now be integrated to build models of how changes in neurochemistry affect physiology. The data are not as strong for the DRD4 or DAT1, although the 9R-allele of a variable nucleotide tandem repeat in the DAT1-gene has been shown to be associated with changes in expression of the gene. A more comprehensive discussion of this gene follows later.

Table 5
fMRI-studies in ADHD by domain

Domain	Studies	Task	Contrast	Results
Response suppression	Baeyens et al. (submitted for publication), Booth et al. (2005), Durston et al. (2003, 2006, 2007), Epstein et al. (2007) (adolescents and adults); Mulder et al. (2008), Schulz et al. (2004, 2005a), Smith et al. (2006), Suskauer et al. (2008), Tamm et al. (2004), Vaidya et al. (1998, 2005)	Go/NoGo	NoGo vs. Go	DLPFC: ADHD < NC (Booth et al., 2005; Epstein et al., 2007 (adolescents only); Mulder et al., 2008); ADHD > NC (Durston et al., 2003). VLPFC: ADHD < NC (Baeyens et al., submitted for publication; Durston et al., 2006, 2007; Epstein et al., 2007; Schulz et al., 2005a (ADHD persists > ADHD remitters > NC)). Secondary motor cortex (pre/supplementary motor): ADHD < NC (Booth et al., 2005; Durston et al., 2006; Suskauer et al., 2008). Precentral gyrus: ADHD < NC (Schulz et al., 2004; Suskauer et al., 2008 (dorsal central section)); ADHD > NC (Suskauer et al., 2008 (more ventromedial WM section)). Orbitofrontal cortex: ADHD < NC (Booth et al., 2005). Anterior PFC (BA10): ADHD < NC (Booth et al., 2005; Durston et al., 2006; Epstein et al., 2007 (adolescents only)); ADHD > NC (Durston et al., 2003; Epstein et al., 2007 (adults only)). Anterior cingulate: ADHD < NC (Booth et al., 2005; Durston et al., 2006, 2007; Mulder et al., 2008; Suskauer et al., 2008). Posterior cingulate: ADHD < NC (Suskauer et al., 2008); ADHD > NC (Durston et al., 2003). Supramarginal gyrus: ADHD < NC (Durston et al., 2006; Epstein et al., 2007 (adolescents only)); ADHD > NC (Durston et al., 2003; Epstein et al., 2007 (adults only)). Inferior parietal lobule: ADHD < NC (Schulz et al., 2005a (ADHD persists > ADHD remitters > NC)). Lingual gyrus: ADHD > NC (Durston et al., 2003); ADHD < NC (Schulz et al., 2004; Schulz et al., 2005a (ADHD persists < ADHD remitters < NC)). Caudate head: ADHD < NC (Booth et al., 2005; Durston et al., 2003). Caudate body: ADHD < NC (Booth et al., 2005; Epstein et al., 2007). Putamen: ADHD < NC (Suskauer et al., 2008). Pallidus: ADHD < NC (Booth et al., 2005). Amygdala: ADHD < NC (Booth et al., 2005). Hippocampus: ADHD < NC (Schulz et al., 2004). Precuneus: ADHD < NC (Suskauer et al., 2008); ADHD > NC (Durston et al., 2003; Epstein et al., 2007 (adults only)). Cuneus: ADHD < NC (Booth et al., 2005; Suskauer et al., 2008). Superior temporal gyrus: ADHD < NC (Suskauer et al., 2008); ADHD > NC (Durston et al., 2003). Inferior temporal gyrus: ADHD < NC (Schulz et al., 2004). Occipital lobe: ADHD < NC (Suskauer et al., 2008). Fusiform gyrus: ADHD < NC (Booth et al., 2005; Suskauer et al., 2008). Medial occipital gyrus: ADHD < NC (Schulz et al., 2005a). Thalamus: ADHD < NC (Booth et al., 2005). Cerebellum: ADHD < NC (Schulz et al., 2004; Suskauer et al., 2008). No differences: Vaidya et al. (2005)
			NoGo vs. oddball trials	OFC: ADHD < NC (Smith et al., 2006 ^a). ACG/Mid cingulate extending into secondary motor cortex and DLPFC: ADHD < NC (Tamm et al., 2004). Temporal cortex: ADHD > NC (Tamm et al., 2004)
			NoGo block vs. reference function	Caudate (% active pixels): ADHD < NC (Vaidya et al., 1998) ^b . Putamen (% active pixels): ADHD < NC (Vaidya et al., 1998) ^b . Prefrontal/cingulate (% active pixels): ADHD > NC (Vaidya et al., 1998) ^b
	Pliszka et al. (2006) and Rubia et al. (2008, 2005)	Stop signal	Successful vs. unsuccessful stop	ACG: ADHD < NC (Pliszka et al., 2006). VLPFC: ADHD < NC (Pliszka et al., 2006; Rubia et al., 2005 (extending into OFC)). DLPFC: ADHD < NC (Rubia et al., 2008). Anterior PFC: ADHD < NC (Rubia et al., 2008). Secondary motor cortex (pre/supplementary motor): ADHD < NC (Rubia et al., 2005). Superior temporal gyrus: ADHD < NC (Rubia et al., 2005)
			Unsuccessful stop vs. go	Posterior cingulate: ADHD < NC (Rubia et al., 2008, 2005). Precuneus: ADHD < NC (Rubia et al., 2008, 2005)

4. Imaging of brain structure and function in ADHD

Magnetic resonance studies of ADHD have often started from a theoretical perspective, where cognitive functions (in functional studies) and brain regions (in anatomical studies) of interest were selected. With the advent of whole-brain voxel-based analysis techniques and resting state fMRI approaches, this is no longer the case, and data-driven approaches can be used to suggest new avenues of theoretical interest.

4.1. Imaging brain function

Problems with cognitive control are the best-established cognitive deficit associated with ADHD (Lijffijt et al., 2005; Nigg et al., 2005). Functional imaging studies have often focused on aspects of this ability using paradigms that require overriding a prepotent response (e.g., go/no-go or stopsignal tasks), ignoring salient information (e.g., flanker and stroop paradigms) or switching from one behavior to another (e.g., switch tasks). Table 5 lists cognitive domains that have been investigated using fMRI in ADHD. The criteria that were used for including studies in

Table 5 (Continued)

Domain	Studies	Task	Contrast	Results
Attention	Booth et al. (2005)	Sustained attention task	High load–low load	Middle temporal gyrus: ADHD < NC (Booth et al., 2005). Fusiform gyrus: ADHD < NC (Booth et al., 2005). Superior parietal/precuneus: ADHD < NC (Booth et al., 2005)
	Konrad et al. (2006, 2007)	Attention network task	Alerting: response cued vs. not cued Reorienting: invalid cued trials vs. valid cued	ACG: ADHD < NC (Konrad et al., 2006). Brainstem: ADHD > NC (Konrad et al., 2006) Putamen: ADHD > NC (Konrad et al., 2006—difference diminished at 1 year follow up when treated with MPH (Konrad et al., 2007)). VLPFC: ADHD > NC (Konrad et al., 2006). Insula: ADHD > NC (Konrad et al., 2006—difference diminished at 1 year follow up when treated with MPH (Konrad et al., 2007)). Temporoparietal junction: at 1 year follow up to Konrad et al. (2006), larger increase in activation in NC than in MPH-treated ADHD (Konrad et al., 2007)
	Schulz et al. (2005b)	Selective/divided attention task	Divided attention vs. baseline	Dorsal striatum: ADHD < NC (Schulz et al., 2005b (ameliorated by methylphenidate)). Middle temporal gyrus: ADHD < NC (Schulz et al., 2005b)
Interference control	Konrad et al. (2006, 2007)	Attention network task	Conflict: incongruent cues vs. congruent flankers	Premotor cortex: ADHD < NC (Konrad et al., 2006). Putamen: ADHD < NC (Konrad et al., 2006). Superior parietal lobule: ADHD > NC (Konrad et al., 2006). ACG: at 1 year follow-up to Konrad et al. (2006), increase in activation larger in NC than in MPH-treated ADHD (Konrad et al., 2007)
	Schulz et al. (2005b)	Stimulus/response conflict task	Stimulus conflict vs. control Combined stimulus/location conflict vs. control	VLPFC: ADHD > NC (Schulz et al., 2005b)
	Vaidya et al. (2005)	Flanker task	Incongruent vs. neutral	VLPFC: ADHD < NC (Vaidya et al., 2005)
	Smith et al. (2006)	Motor stroop	Stroop vs. oddball trials	No differences (Smith et al., 2006)
Vigilance	Rubia et al. (2007) and Stevens et al. (2007)	Auditory oddball	Oddball vs. standard	Middle/superior temporal: ADHD < NC (Rubia et al., 2007 (large clusters including striatal and thalamic regions as well)); Stevens et al., 2007). DLPFC: ADHD < NC (Stevens et al., 2007). Supramarginal gyrus: ADHD < NC (Rubia et al., 2007). Posterior cingulate: ADHD < NC (Rubia et al., 2007)
		Standard vs. oddball	ACG: ADHD < NC (Rubia et al., 2007). Ventromedial cortex: ADHD < NC (Rubia et al., 2007). DLPFC: ADHD < NC (Rubia et al., 2007)	
		Novel vs. oddball	Inferior parietal lobule/supramarginal gyrus: ADHD < NC (Stevens et al., 2007). Superior temporal gyrus: ADHD < NC (Stevens et al., 2007)	
	Tamm et al. (2006)	Visual oddball task	Oddball vs. standard	Cluster of inferior parietal lobule, supramarginal and angular gyrus: ADHD < NC (Tamm et al., 2006). Precuneus/cuneus: ADHD < NC (Tamm et al., 2006). Cluster of thalamus and Mid cingulate: ADHD < NC (Tamm et al., 2006)
Working memory	Sheridan et al. (2007)	Delayed matching to sample	Encoding high load vs. low load	VLPFC: ADHD < NC (Sheridan et al., 2007 (extending to insula)). Inferior parietal lobule: ADHD < NC (Sheridan et al., 2007)
	Valera et al. (2005)	N-Back	2-Back vs. control	Cerebellum (posterior lobe): ADHD < NC (Valera et al., 2005). Inferior occipital gyrus: ADHD < NC (Valera et al., 2005)
	Hale et al. (2007) (adults)	Digit span	Forward vs. baseline	Temporal/occipital border: ADHD > NC (Hale et al., 2007). Precuneus/cuneus: ADHD > NC (Hale et al., 2007). Mid/posterior cingulate: ADHD > NC (Hale et al., 2007). DLPFC: ADHD > NC (Hale et al., 2007). VLPFC: ADHD > NC (Hale et al., 2007)
		Backward vs. baseline	Superior parietal lobule: ADHD < NC (Hale et al., 2007). Intraparietal sulcus: ADHD < NC (Hale et al., 2007). Supramarginal gyrus: ADHD < NC (Hale et al., 2007). Temporal/occipital border: ADHD < NC (Hale et al., 2007). Angular gyrus: ADHD > NC (Hale et al., 2007). Superior temporal sulcus: ADHD > NC (Hale et al., 2007). Mid cingulate gyrus: ADHD > NC (Hale et al., 2007)	
Silk et al. (2005) and Vance et al. (2007)	Mental rotation	Rotation vs. baseline	Caudate: ADHD < NC (Silk et al., 2005; Vance et al., 2007). Anterior PFC: ADHD < NC (Silk et al., 2005). DLPFC: ADHD < NC (Silk et al., 2005). VLPFC: ADHD < NC (Silk et al., 2005). Parieto/occipito/temporal association cortex: ADHD < NC (Silk et al., 2005). Mid/Sup temporal gyri: ADHD > NC (Silk et al., 2005). Posterior cingulate: ADHD > NC (Silk et al., 2005). Frontal cluster (BA8–10): ADHD > NC (Silk et al., 2005). Precuneus/cuneus: ADHD < NC (Vance et al., 2007). Inferior parietal: ADHD < NC (Vance et al., 2007)	
Episodic memory	Krauel et al. (2007)	Emotional pictures recognition task	Remembered vs. forgotten pictures Neutral pictures: remembered vs. forgotten	Inferior parietal lobule/Supramarginal gyrus: ADHD > NC (Krauel et al., 2007). Precuneus: ADHD > NC (Krauel et al., 2007). Superior parietal lobule: ADHD > NC (Krauel et al., 2007). Precuneus: ADHD > NC (Krauel et al., 2007). Superior parietal lobule: ADHD > NC (Krauel et al., 2007). Insula: ADHD > NC (Krauel et al., 2007). Superior temporal gyrus: ADHD > NC (Krauel et al., 2007). Superior occipital gyrus: ADHD > NC (Krauel et al., 2007). Secondary motor cortex (pre/supplementary motor): ADHD > NC (Krauel et al., 2007). ACG: ADHD < NC (Krauel et al., 2007)

Table 5 (Continued)

Domain	Studies	Task	Contrast	Results
Timing/expectancy	Durston et al. (2007) and Mulder et al. (2008)	Adapted Go/NoGo	Unexpected vs. expected stimulus timing	Cerebellum: ADHD < NC (Durston et al., 2007; Mulder et al., 2008)
Emotional processing	Marsh et al. (2008)	Facial expressions task	Fear vs. neutral Angry vs. neutral	No differences between ADHD and NC Middle frontal gyrus at border BA8 and BA6: ADHD > NC (Marsh et al., 2008). Inferior temporal gyrus: ADHD > NC (Marsh et al., 2008). Posterior cingulate: ADHD > NC (Marsh et al., 2008)
Motor	Mostofsky et al. (2006)	Finger tapping	Tapping vs. rest	Supramarginal gyrus: ADHD < NC (Mostofsky et al., 2006). Primary somatosensory cortex: ADHD < NC (Mostofsky et al., 2006). Superior parietal lobule: ADHD < NC (Mostofsky et al., 2006)
Reward	Baeyens et al. (submitted for publication), Scheres et al. (2007) and Strohle et al. (2008) (adults)	Monetary incentive delay task	Gain vs. no gain (anticipation) Gain vs. no gain (outcome)	Ventral striatum/caudate: ADHD < NC (Baeyens et al., submitted for publication) (no interaction with cognitive control performance); Scheres et al., 2007; Strohle et al., 2008). Superior temporal gyrus: ADHD < NC (Baeyens et al., submitted for publication) OFC: ADHD > NC (Strohle et al., 2008). VLPFC: ADHD > NC (Strohle et al., 2008). DLPFC and Anterior PFC: ADHD > NC (Strohle et al., 2008). Caudate/lentiform nucleus: ADHD > NC (Strohle et al., 2008)
Resting state	Cao et al. (2006) and Uddin et al. (2008) (adults)	BOLD signal based	Regional/network homogeneity	Inferior frontal gyrus (ventrolateral prefrontal cortex): ADHD < NC (Cao et al., 2006). Anterior cingulate: ADHD < NC (Cao et al., 2006). Caudate: ADHD < NC (Cao et al., 2006). Pyramis: ADHD < NC (Cao et al., 2006). Precuneus: ADHD < NC (Cao et al., 2006; Uddin et al., 2008 (as part of default mode network)). Lingual gyrus: ADHD > NC (Cao et al., 2006). Cuneus: ADHD > NC (Cao et al., 2006). Culmen: ADHD > NC (Cao et al., 2006). Parahippocampal gyrus: ADHD > NC (Cao et al., 2006)
	Wang et al., 2008	BOLD signal based	Small world networks approach	No significant differences in global efficiency of networks, however ADHD increased local networks efficiency (Wang et al., 2008). Decreased efficiency of network nodes in OFC, VMPFC, lingual gyrus, calcarine cortex, middle/inferior temporal gyrus and temporal pole (Wang et al., 2008). Increased nodal efficiency in VLPFC and pallidum (Wang et al., 2008)
	Castellanos et al. (2008) and Tian et al. (2006)	BOLD signal based	Seed based correlational	ADHD < NC connectivity between ACG and PCG/precuneus and between precuneus and VMPFC and PCG (Castellanos et al., 2008). ADHD > NC connectivity between dorsal ACG and posterior cingulate, thalamus, insula, brainstem/pons and cerebellum. (Tian et al., 2006)
	Zang et al. (2007)	BOLD signal based	Voxelwise comparison of low frequency fluctuation amplitude	Brainstem: ADHD > NC (Zang et al., 2007). Cluster cerebellum/fusiform gyrus: ADHD > NC (Zang et al., 2007). VLPFC: ADHD < NC (Zang et al., 2007). Inferior temporal gyrus: ADHD > NC (Zang et al., 2007). Sensorimotor cortex: ADHD > NC (Zang et al., 2007). Cerebellum (lobes and vermis): ADHD < NC (Zang et al., 2007). ACG: ADHD > NC (Zang et al., 2007). Pons: ADHD > NC (Zang et al., 2007)
	Tian et al. (2008)	BOLD signal based	Resting state activity index	Cuneus/lingual gyrus: ADHD > NC (Tian et al., 2008). Thalamus/dorsal brainstem/midbrain: ADHD > NC (Tian et al., 2008). Postcentral gyrus: ADHD > NC (Tian et al., 2008). Superior temporal gyrus: ADHD > NC (Tian et al., 2008)
	Teicher et al. (2000)	T2 relaxometry ^c		Putamen: ADHD > NC (Teicher et al., 2000). Caudate: no differences (Teicher et al., 2000). Thalamus: no differences (Teicher et al., 2000)

ACG, anterior cingulate gyrus; DLPFC, dorsolateral prefrontal cortex; Mid, middle; NC, normal controls; OFC, orbito-frontal cortex; PFC, prefrontal cortex; PCG, posterior cingulate gyrus; Sup, superior; TG, temporal gyrus; VLPFC, ventrolateral prefrontal cortex.

^a No talairach/MNI coordinates reported, labelling of regions is from authors for this study.

^b In the study by Vaidya et al. (1998), striatal effects were seen in the stimulus controlled version of the task (number of stimulus presentations per block controlled) but not in the response controlled version of the task (number of key presses per block controlled). The prefrontal/cingulate differences however were observed only in the response controlled version rather than the stimulus controlled version of the task.

^c Increased T2-relaxation time is associated with decreased blood perfusion, pointing to decreased activity over time in the steady state.

this table are described in the Methods section. It is not an exhaustive overview of the literature, as other, more comprehensive reviews are available (Bush et al., 2005; Casey and Durston, in press; Durston, 2003). From the table, it is obvious that cognitive control is the most investigated domain, although it is not the only one. At a first glance, the widely diverse findings appear too disparate to be informative in terms of underlying neurobiological changes. However, a common theoretical framework can be discerned: many of the tasks involve aspects of cognitive control. For example, a working memory task such as the *N*-back is not typically conceptualized as a cognitive control task. However, it does involve aspects of this ability, as it requires the subject to override the obvious response to a stimulus (i.e., press the button

corresponding to the stimulus on the screen) and rather to react to a stimulus that occurred one or more trials ago. Similar arguments can be made for many of the cognitive tasks listed in Table 5. As, such, many of the studies showing reduced activity in frontostriatal dopamine circuits involve aspects of this ability. Other changes in brain activity are reported, depending on the nature of the task: for example, tasks involving vigilance have shown (additional) changes in temporal regions (Rubia et al., 2007) and working memory tasks have shown changes in more dorsolateral prefrontal regions (Sheridan et al., 2007). These different studies all focus on different aspects of cognitive functioning, but as cognitive (and neural) processes are intrinsically linked, deficits in one system are likely to affect others in secondary ways (see also

Chambers et al., this issue for a more comprehensive discussion). An interesting and relatively new direction in functional neuroimaging of ADHD is an interest in reward-related circuitry. This follows from theoretical accounts of ADHD that attribute importance to reward in this disorder and relate changes in sensitivity to reinforcement to symptoms of hyperactivity and impulsivity (Sagvolden et al., 1998; Sonuga-Barke, 2002). These studies have shown reduced activity in ventral striatum in response to reward (Scheres et al., 2007; Strohle et al., 2008).

Studies using resting state approaches are not tied to a theoretical vantage point in the same way as studies that choose a paradigm to tax a particular function in ADHD. In these studies, fMRI scans are typically acquired while the subject lies quietly with his/her eyes closed. The resulting images can then be used to investigate synchronization of activity in neural circuits in rest. These patterns of activity have been shown to correlate with behavioral and cognitive measures and could potentially lead to task-independent biomarkers of neuropsychiatric disorders (Greicius, 2008; Kelly et al., 2007). Such an a-theoretical approach may be advantageous as such investigations can provide unexpected results, suggesting new

directions for research. However, a caveat is that these approaches do not have the constraint of task performance, allowing researchers to monitor what the subject is doing while in the scanner. It is noteworthy that this very different approach has shown changes in some of the same fronto-striatal regions that have been reported using more traditional fMRI-designs.

4.2. Imaging brain structure

Studies of brain structure can also take a data-driven approach to investigating ADHD: for example, whole-brain voxel-based methods search for differences between groups throughout the brain without requiring a priori hypotheses of where they may be found. In contrast, studies using volumetric approaches of necessity take a more theoretically driven approach, as they must select the regions to compare between groups. Studies of brain structure in ADHD are listed in Table 6, by the approach taken. It is not an exhaustive overview and other, more comprehensive reviews and a meta-analysis are available in the literature (Durston, 2003; Seidman et al., 2005; Valera et al., 2007) Studies

Table 6
Results from MR-studies of brain structure by approach

Approach	Studies	ROI	Results
Manual and (semi-)automated ROI	Aylward et al. (1996), Baumgardner et al. (1996), Berquin et al. (1998), Bussing et al. (2002), Castellanos et al. (1994, 1996a,b, 2001, 2002, 2003) (discordant MZ twins), Durston et al. (2004), Filipek et al. (1997), Giedd et al. (1994), Hessleringer et al. (2002) (adults), Hill et al. (2003), Hynd et al. (1991, 1993), Kates et al. (2002), Lyoo et al. (1996), Mackie et al. (2007), Mataro et al. (1997), Mostofsky et al. (1998, 2002), Overmeyer et al. (2000), Pineda et al. (2002), Plessen et al. (2006), Seidman et al. (2006) (adults), Semrud-Clikeman et al. (1994, 2000, 2006), Uhlikova et al. (2007), Wellington et al. (2006) and Wolosin et al. (in press)	Total brain Corpus callosum Pallidum Caudate nucleus Putamen Nucleus accumbens ACG Posterior cingulate Hippocampus Amygdala Thalamus Ventricles Frontal lobe	ADHD < NC (Berquin et al., 1998; Castellanos et al., 2001, 1994, 1996b, 2002; Hill et al., 2003; Mostofsky et al., 2002; Seidman et al., 2006; Wolosin et al., in press). ADHD = NC (Bussing et al., 2002; Hessleringer et al., 2002; Kates et al., 2002 (at trend ADHD < NC); Lyoo et al., 1996; Overmeyer et al., 2000; Seidman et al., 2006). ICV: ADHD < NC (Durston et al., 2004). GM: ADHD < NC (Castellanos et al., 2002; Mostofsky et al., 2002; Seidman et al., 2006). WM: ADHD < NC (Castellanos et al., 2002; Mostofsky et al., 2002). ADHD > NC (Seidman et al., 2006) ADHD < NC (Hill et al., 2003). ADHD = NC (Castellanos et al., 1996b; Overmeyer et al., 2000). Body: ADHD < NC (Baumgardner et al., 1996; Giedd et al., 1994). Genu: ADHD < NC (Giedd et al., 1994, rostrum; Hynd et al., 1991). Isthmus: ADHD < NC (Lyoo et al., 1996). Splenium: ADHD < NC (Hill et al., 2003; Hynd et al., 1991; Lyoo et al., 1996; Semrud-Clikeman et al., 1994) ADHD < NC (Aylward et al., 1996; Castellanos et al., 2001). ADHD = NC (Castellanos et al., 1996b; Seidman et al., 2006). Reversed asymmetry (Castellanos et al., 1996a; Uhlikova et al., 2007) ADHD < NC (Castellanos et al., 1994; Castellanos et al., 1996b, 2001, 2002, 2003; Filipek et al., 1997; Hynd et al., 1993 ^a ; Semrud-Clikeman et al., 2000; Semrud-Clikeman et al., 2006). ADHD > NC (Mataro et al., 1997, one slice area). ADHD = NC (Aylward et al., 1996; Bussing et al., 2002; Castellanos et al., 1996a; Pineda et al., 2002 ^{a,b} ; Hill et al., 2003; Seidman et al., 2006). Reversed asymmetry (Castellanos et al., 1994; Hynd et al., 1993 ^a ; Uhlikova et al., 2007) ADHD = NC (Aylward et al., 1996; Castellanos et al., 1996a; Castellanos et al., 1996b; Castellanos et al., 2001; Seidman et al., 2006; Uhlikova et al., 2007; Wellington et al., 2006). Reversed asymmetry (Wellington et al., 2006) ADHD > NC (Seidman et al., 2006) ADHD < NC (Seidman et al., 2006; Semrud-Clikeman et al., 2006, difference not found in medicated children). ADHD = NC (Kates et al., 2002; Mostofsky et al., 2002) ADHD = NC (Seidman et al., 2006) ADHD > NC (Plessen et al., 2006, mainly attributable to enlarged head of hippocampus). ADHD = NC (Castellanos et al., 1996b; Filipek et al., 1997; Seidman et al., 2006) ADHD < NC (Castellanos et al., 1996b). ADHD = NC (Filipek et al., 1997; Plessen et al., 2006, detailed analyses did show reduced basolateral complex in ADHD; Seidman et al., 2006) ADHD = NC (Seidman et al., 2006) ADHD > NC (Lyoo et al., 1996). ADHD = NC (Castellanos et al., 1996b; Filipek et al., 1997; Seidman et al., 2006) ADHD < NC (Castellanos et al., 1996b, 2001, 2002; Filipek et al., 1997; Semrud-Clikeman et al., 2000; Mostofsky et al., 2002; Seidman et al., 2006). ADHD = NC (Castellanos et al., 2003). Deep WM: ADHD < NC (Kates et al., 2002; Mostofsky et al., 2002). Orbitofrontal cortex: ADHD < NC (Hessleringer et al., 2002; Plessen et al., 2006). Prefrontal cortex: ADHD < NC (Durston et al., 2004; Kates et al., 2002; Mostofsky et al., 2002; Seidman et al., 2006). Premotor cortex: ADHD < NC (Mostofsky et al., 2002). Superior frontal gyrus: ADHD < NC (Hill et al., 2003)

Table 6 (Continued)

Approach	Studies	ROI	Results
		Parietal lobe	ADHD < NC (Castellanos et al., 2002; Filipek et al., 1997; Wolosin et al., in press).
		Temporal lobe	ADHD = NC (Castellanos et al., 2003; Durston et al., 2004; Seidman et al., 2006)
		Occipital lobe	ADHD < NC (Castellanos et al., 2002; Durston et al., 2004; Wolosin et al., in press).
		Insula	ADHD = NC (Castellanos et al., 2003; Seidman et al., 2006)
		Brainstem	ADHD = NC (Filipek et al., 1997)
		Cerebellum	ADHD = NC (Lyoo et al., 1996)
			ADHD < NC (Castellanos et al., 1996b, 2001, 2002; Durston et al., 2004). ADHD = NC (Castellanos et al., 2003; Lyoo et al., 1996; Seidman et al., 2006). Vermis: ADHD < NC (Berquin et al., 1998; Bussing et al., 2002; Castellanos et al., 2001; Mackie et al., 2007; Mostofsky et al., 1998). ADHD = NC (Hill et al., 2003). Lobules: ADHD < NC (Berquin et al., 1998; Hill et al., 2003; Mostofsky et al., 1998). Progressive decrease in worse clinical outcome ADHD (Mackie et al., 2007)
Whole brain voxelbased approaches ^c	Brieber et al. (2007), Carmona et al. (2005), McAlonan et al. (2007), Overmeyer et al. (2001) and Wang et al. (2007)		Basal ganglia: ADHD < NC (Brieber et al., 2007; McAlonan et al., 2007; Overmeyer et al., 2001; Wang et al., 2007). Cerebellum: ADHD < NC (Carmona et al., 2005; McAlonan et al., 2007). Cingulate cortex: ADHD < NC (Overmeyer et al., 2001). ADHD > NC (Brieber et al., 2007). Hippocampus: ADHD < NC (Brieber et al., 2007). Insula: ADHD < NC (Brieber et al., 2007). Occipital lobe: ADHD < NC (Brieber et al., 2007; McAlonan et al., 2007). ADHD > NC (Wang et al., 2007). Parietal lobe: ADHD < NC (McAlonan et al., 2007; Wang et al., 2007). ADHD > NC (Brieber et al., 2007). Prefrontal cortex: ADHD < NC (Brieber et al., 2007; Carmona et al., 2005; McAlonan et al., 2007; Overmeyer et al., 2001; Wang et al., 2007). Motor/premotor cortex: ADHD < NC (Carmona et al., 2005). Temporal cortex: ADHD < NC (Brieber et al., 2007; Wang et al., 2007). Ventricles (posterior lateral): ADHD > NC (Wang et al., 2007)
Cortical thickness	Shaw et al. (2006), Shaw et al. (2007a), Sowell et al. (2003), Li et al. (2007), Makris et al. (2007a) (adults) and Wolosin et al. (in press)		Mean cortical thickness: ADHD < NC (Shaw et al., 2006); ADHD = NC (Wolosin et al., in press). Total cortical folding/surface area: ADHD < NC (Wolosin et al., 2005; in press). Age at peak cortical thickness: ADHD < NC (3 years delay, most pronounced in frontal cortex, Shaw et al., 2007a,b). Cingulate cortex: ADHD < NC (Makris et al., 2007a,b). DLPFC: ADHD < NC (Makris et al., 2007a,b; Shaw et al., 2006; Sowell et al., 2003). OFC: ADHD < NC (Makris et al., 2007a,b). Prefrontal cortex convolution complexity: ADHD < NC (Li et al., 2007). Precentral cortex: ADHD < NC (Shaw et al., 2006). Occipital cortex: ADHD > NC (Sowell et al., 2003). Parietal cortex: ADHD < NC (Makris et al., 2007a,b; Sowell et al., 2003; Wolosin et al., in press); ADHD > NC (Sowell et al., 2003). Temporal cortex: ADHD < NC (Shaw et al., 2006; Sowell et al., 2003); ADHD > NC (Sowell et al., 2003 ^d)
Diffusion tensor imaging	Ashtari et al. (2005) and Makris et al. (2007b) (adults)		FA: ADHD < NC in anterior internal capsule, fronto-cortico-striatal and cerebral peduncle, cerebellar peduncle, occipito-parietal WM (Ashtari et al., 2005), cingulum bundle and superior longitudinal fasciculus (Makris et al., 2007a,b)

ACG, anterior cingulate gyrus; DLPFC, dorsolateral prefrontal cortex; FA, fractional anisotropy; GM, gray matter; ICV, intracranial volume; MZ, monozygotic; OFC, orbito-frontal cortex; NC, normal controls; WM, white matter.

^a Scans were not realigned before segmentation.

^b Uncorrected for total brain volume.

^c Results for the voxelbased approaches do not refer to differences in volume, but to differences in GM density, as assessed by these techniques.

^d This result refers to increased grey matter density measures devised in a different way than in studies using voxelbased morphometry. Other results from Sowell et al. (2003) study pertain differences in brain surface extent.

using data-driven, whole-brain approaches have shown changes in a wide variety of regions, including fronto-striatal areas that would be predicted from deficits in cognitive control. Other regions that show changes in ADHD include areas in cingulate cortex (Brieber et al., 2007; Carmona et al., 2005; Overmeyer et al., 2001), all other major cortical lobes (occipital, parietal and temporal cortex) (Brieber et al., 2007; Carmona et al., 2005; McAlonan et al., 2007; Wang et al., 2007) and the medial temporal lobe (Brieber et al., 2007; Carmona et al., 2005). Studies using cortical thickness measures have similarly shown changes throughout the cortex, with the most striking differences between children with ADHD and controls perhaps in the developmental trajectories, where children with ADHD show a lag in cortical development of several years, particularly in prefrontal areas (Shaw et al., 2007a). Studies defining regions of interest from a theoretical approach have consistently shown smaller than average total brain volumes in ADHD, as well as smaller volumes of fronto-striatal regions and changes in cerebellum (see Table 6). Studies that have looked at the volume of other cortical lobes have sometimes shown reductions in volume here too (Durston et al., 2004; Filipek et al.,

1997; Wolosin et al., in press). Interestingly, the volume of the medial temporal lobe structures has also been reported to differ between children with ADHD and control subjects (Castellanos et al., 1996b; Plessen et al., 2006), although in one case total hippocampus was reported to be larger in ADHD while only the posterior sections were smaller (Plessen et al., 2006). It is interesting that these structures have been implicated using both hypothesis- and data-driven approaches. These changes could be related to symptoms of anxiety or aggression in ADHD and may suggest new directions for imaging genetics in this disorder, as will be discussed later.

5. Imaging heritability and genes in ADHD

ADHD is a highly heritable disorder (Tables 2–4) and its neurobiological basis is well understood, at least in terms of cognitive control (Tables 5–6). As such, this disorder appears to be a strong candidate for investigation using an endophenotype approach, such as outlined in the Introduction (see also Aron and Poldrack, 2005). To date, there is very limited data available on the

Table 7
Studies imaging genetics in ADHD

Authors	Participants <i>N</i> (subtype), #males, age (years)	Design imaging modality (field strength), processing and regions of interest, genes	Results
Castellanos et al. (1998)	41 ADHD, not given, <i>M</i> (S.D.) = 9.7 (2.6). 57 NC, not given, <i>M</i> (S.D.) = 17.6 (9.1)	Structural MRI (1.5 T). Semi-automated volume TB, cerebellum, PFC manual volume CN, PAL. DRD4 VNTR exon3: carriers 7R vs. non-carriers	No genotype effects. No group × genotype interactions
Bobb et al. (2005)	163 ADHD (6% I, 94% C), 53%, <i>M</i> (S.D.) = 9.0 (2.2). 129 NC, 57%, <i>M</i> (S.D.) = 16.0 (8.1)	Structural MRI (1.5 T) T1 SPGR. Fully automated volume TB, lobes, basal ganglia, cerebellum. DRD1 (C allele of rs4532 vs. other and T allele of rs265981 vs. other) NET1 (C allele of rs998424 vs. other and T allele of rs3785157 vs. other)	No genotype effects. No group × genotype interactions
Durston et al. (2005)	30 ADHD (17% I, 13% HI, 70% C), all male, <i>M</i> (S.D.) = 12.1 (2.5). 30 unaffected siblings, all male, <i>M</i> (S.D.) = 11.6 (3.2). 30 NC, all male, <i>M</i> (S.D.) = 10.7 (1.9)	Structural MRI (1.5T). Automated volume of PFC GM manual volume of CN. DRD4 VNTR exon 3: carrier variant allele vs. homozygous 4R. DAT1 VNTR: carrier 9R vs. homozygous 10R	Main effects: DAT1: CN 9R > 10R; DRD4: PFC GM 4R < variant alleles
Shaw et al. (2007,b)	43 ADHD 7R (54% I, 7% HI, 21% C, 18% in remission), 53%, <i>M</i> (S.D.) = 10.2 (2.7) (at initial scan). 62 ADHD non-7R (18% I, 4% HI, 51% C, 21% in remission), 44%, <i>M</i> (S.D.) = 10.1 (2.9) (at initial scan). 35 NC 7R, 49%, <i>M</i> (S.D.) = 10.3 (2.8) (at initial scan). 68 NC non-7R, 60%, <i>M</i> (S.D.) = 10.0 (2.9) (at initial scan)	Structural MRI (1.5T), T1 SPGR. Fully automated cortical thickness. DRD4 VNTR on exon 3: carriers 7R vs. non-carriers	Main effect diagnosis: ADHD < NC in OFC, sup/med PFC and post parietal cortex. Main effect of DRD4 7R allele in similar regions: ADHD 7R < ADHD non-7R < NC 7R < NC non-7R
Durston et al. (2008)	10 ADHD (10% HI, 90% C), all male, <i>M</i> (S.D.) = 14.6 (2.6). 10 unaffected sibs, all male, <i>M</i> (S.D.) = 14.8 (2.3). 9 NC, all male, <i>M</i> (S.D.) = 15.3 (2.1)	fMRI 3D-PRESTO (1.5 T) with parametric Go/NoGo task. Whole-brain analysis of genotype. DAT1 VNTR: 9R carriers vs. homozygous 10R	Main effect genotype: 9R ↑ activation in CN 9R ↓ activation in vermis. Group × genotype interaction: effect in CN due to ADHD and unaffected siblings—not NC

CN, caudate nucleus; GM, gray matter; *M*, mean; med, medial; NC, normal controls; OFC, orbitofrontal cortex; PFC, prefrontal cortex; PAL, pallidum; post, posterior; S.D., standard deviation; sup, superior; TB, total brain.

heritability of brain structure and activity in ADHD. Anatomical (and to a lesser extent functional) MR studies have investigated heritability of the brain in healthy adults and typical development using twin-pair approaches (e.g., Blokland et al., 2008; Hulshoff Pol et al., 2002, 2006; Lenroot et al., 2007; Matthews et al., 2007; Polk et al., 2007; Schmitt et al., 2008). By comparing correlations in monozygotic and dizygotic twins, these studies are able to estimate the heritability of various brain measures. In ADHD, the only study to date to look at brain structure in twin pairs did not estimate heritability, but rather compared discordant monozygotic twin pairs to show that caudate volume was reduced in the probands (Castellanos et al., 2003). We have used a discordant sibling pair approach in ADHD, as similarities in full siblings can give a sense of whether brain changes are under heritable influences (Durston et al., 2004, 2006). However, this approach does not allow for an estimate of heritability in the same way that a twin-pair design does.

The first study to investigate gene effects on brain anatomy in ADHD did so a decade ago, in 1998 (Castellanos et al., 1998). Castellanos and colleagues investigated the 7R allele of the most frequently investigated VNTR of the DRD4 gene, located on exon 3. They looked at a number of brain regions and found no significant effects of genotype. In another study, two genes were selected, the DRD1 and NET1, and their effects on a large number of brain regions were investigated. Again, no effects survived the correction for multiple comparisons (Bobb et al., 2005). These initial efforts were somewhat disappointing, given that ADHD seems a strong candidate for such an approach. Recently, investigators have taken a different approach to investigating gene effects in ADHD: potential endophenotypes are selected based on criteria outlined in Table 1, candidate genes are selected based on a number of criteria and, crucially, clear and testable hypotheses are defined. In the next section on imaging genetics using cognitive control as an endophenotype, we outline this approach. Table 7 lists studies of imaging genetics in ADHD.

5.1. Imaging genetics of cognitive control in ADHD

Neuroimaging measures of cognitive control are a strong candidate endophenotype for imaging genetics in ADHD, as they meet most of the criteria listed in Table 1: behavioral measures of cognitive control can be continuously quantified, using go-no/go and stop-paradigms (criterion 1). The same applies to neuroimaging measures. Deficits in cognitive control are stable and probably the best-established deficit associated with ADHD (Nigg et al., 2005; criteria 2 and 4). Changes in cognitive control have been shown in both affected and unaffected siblings of individuals with ADHD, suggesting they cluster in families with the disorder and affect family-members without ADHD (Slaats-Willemse et al., 2003; criteria 6 and 7). Finally, Neuroimaging studies have shown structural changes in fronto-striatal dopamine circuits, as well as functional changes during tasks that tax cognitive control. As such, deficits in this ability in ADHD are firmly grounded in neuroscience (criterion 8). In sum, cognitive control and associated brain circuits form a promising endophenotype for investigating genetic influences in ADHD.

We have conducted a series of four studies investigating cognitive control as an endophenotype for genetic effects in ADHD. We have taken the approach of first showing that changes in brain structure and function associated with cognitive control are also found in unaffected family members of individuals with ADHD (criterion 7). To achieve this, we have selected male sibling pairs who are truly discordant for ADHD: probands meet criteria for the disorder by structured parent interview (Diagnostic Interview Schedule for Children (DISC-P); Schaffer et al., 2000) and parent and teacher rating scales (Child Behavior Checklist (CBCL) and Teacher Report Form (TRF); Achenbach and Rescorla, 2001). Discordant siblings are truly free of ADHD symptoms and do therefore not have sub-threshold symptoms of the disorder. A third group of control subjects is included, with no first-degree relatives with psychiatric diagnoses. When deficits in dopamine cognitive

control circuits had been established, we moved on to investigate effects of established ADHD risk genes on these measures. To avoid large number of comparisons, we added three further criteria: genes were selected if they were (1) true candidate genes that had been frequently replicated and preferably shown to be associated with ADHD in meta-analyses, (2) had expression patterns in the brain that led to testable hypotheses in terms of neuroimaging and (3) these expression patterns were associated with fronto-striatal circuits implicated in cognitive control.

In our first study of brain anatomy, we included 30 discordant sibling pairs and 30 controls (Durston et al., 2004). We found widespread, but subtle reductions of cortical gray matter in both affected and unaffected siblings, with effect most pronounced in the prefrontal lobe. Interestingly, the only region that differentiated between affected and unaffected siblings was the cerebellum, where volume (of the right hemisphere) was reduced for affected but not unaffected siblings. In a second study, we investigated changes in brain function associated with cognitive control, using a similar design (Durston et al., 2006). Eleven discordant sibling pairs and 11 control subjects participated in an fMRI-study, where they performed a go/no-go paradigm. Boys with ADHD were impaired in their performance on the most difficult trials, whereas unaffected siblings were not. However, both unaffected and affected siblings showed reduced activation in ventral prefrontal cortex, a region that is critical to performance of this task (Durston and Casey, 2006). Interestingly, unaffected siblings showed a correlation between activity in this region and task performance, similar to controls, whereas boys with ADHD did not. As both studies showed that some of the brain changes in cognitive control circuits in ADHD were shared by unaffected relatives (criterion 7), we moved on to investigate the effect of candidate genes on these brain regions. Based on the three criteria outlined in the previous paragraph, we selected two genes, the DRD4 and the DAT1 genes (see Tables 2 and 4). In the first study we investigated the effect of these genes on fronto-striatal volumes. We hypothesized that these genes would affect the regions where they are preferentially expressed in the brain: prefrontal cortex for the DRD4 and striatum for the DAT1. We found that this was indeed the case, as carriers of the DAT1 9R-allele had smaller average caudate nucleus volume and carriers of a variant DRD4-allele showed changes in volume of prefrontal gray matter (Durston et al., 2005). There was dissociation between the effects of these genes, as there were no effects of the DAT1-gene on prefrontal volume or of the DRD4-gene on caudate nucleus. In a large, independent study, Shaw and colleagues further advanced the investigation of DRD4 effects by using a fine-mapping approach to show differences in cortical thickness between carriers of the 7R-allele of the VNTR and non-carriers. They showed effects in prefrontal cortex, in line with our hypothesis-driven findings (Shaw et al., 2007b). Interestingly, they also reported differences in parietal cortex, in line with reports of DRD4 expression throughout the cortex (Table 4). In a second study of gene effects on brain activity during a cognitive control task, we chose to investigate only one gene, due to the smaller number of subjects in this study. We chose to investigate the DAT1-gene, as we could make clear predictions of genotype effects based on literature on effects of methylphenidate (MPH) on brain activity: MPH blocks the dopamine transporter in vivo (Volkow et al., 1998). In functional studies, MPH has been associated with normalization of activity in striatum for individuals with ADHD (Vaidya et al., 1998) and increased activity in the vermis of the cerebellum (Schweitzer et al., 2003). We hypothesized that DAT1-genotype would mirror MPH-effects on brain activity, with the lower expressing allele being associated with less transporter available in the synapse and therefore increased activity in striatum and the

vermis. Although the VNTR-polymorphism of the DAT1-gene has been shown to affect expression of the transporter in vitro (Fuke et al., 2001; Mill et al., 2002) and in vivo (Heinz et al., 2000; Jacobsen et al., 2000; Lynch et al., 2003; Martinez et al., 2001; Van Dyck et al., 2005), results have been somewhat contradictory in terms of the direction of the association. For example, in vivo studies have reported greater DAT availability for the 9R-allele (Jacobsen et al., 2000; Van Dyck et al., 2005), the 10R-allele (Heinz et al., 2000) and no difference (Lynch et al., 2003; Martinez et al., 2001). The in vitro work to date has produced similar disparate results. Therefore, perhaps the most convincing evidence for the direction of the effect comes from clinical observations: the 9R-allele has been associated with cocaine-induced paranoia, severity of alcohol withdrawal symptoms and a reduced risk of tobacco smoking—all phenomena that are associated with increased synaptic dopamine availability (see Van Dyck et al., 2005). Therefore, we predicted that it would be the 9R-allele that was associated increased activity compared to the 10R-allele.

This is indeed what we found in the striatum (Durston et al., 2008): in this region, carriers of the 9R-allele showed greater activity on cognitive control trials than individuals homozygous for the 10R-allele. For the vermis, we found the opposite pattern. Furthermore, we found an interaction between familial risk and DAT1-genotype in striatum, where individuals at risk of ADHD (probands and unaffected siblings) showed the effect of DAT1-genotype, but control subjects did not. This suggests that this region may be involved in translating the risk conveyed by a DAT1 risk-allele into a neurobiological substrate (changed activity) for those individuals at risk (Durston et al., 2008). The interpretation of these findings is complex, as it is the 10R-allele that has been associated with a diagnosis of ADHD. Furthermore, from a quantitative trait perspective a common variant like the 10R would be expected to influence striatal activation in control subjects. This has been shown for other genes, such as COMT on prefrontal activity (e.g., Tan et al., 2007; Winterer et al., 2006) and for the DAT1 gene in striatum in adults (Schott et al., 2006). In our study, the sample size may not have been sufficient to detect DAT1 effects in controls. A true endophenotype would be expected to show greater penetrance of genetic effects in at-risk individuals, which would explain why we did detect effects in the affected and unaffected siblings. Clearly, carrying the DAT1 risk-allele is not sufficient to develop ADHD by itself, as the effect was found in unaffected family members as well. However, these results do show how we may begin to visualize genetic effects at work in the brain.

The findings above show that neuroimaging measures of cognitive control are a useful endophenotype in investigating dopamine gene effects in ADHD. They illustrate the value of establishing the validity of endophenotypes before using them in the investigation of gene effects. Furthermore, they show how knowledge of gene expression pattern can be used to establish clear and testable hypotheses, thus avoiding great numbers of comparisons that require strict statistical corrections.

5.2. Other leads in imaging genetics in ADHD: the cerebellum

In this section, we briefly consider other candidate systems as endophenotypes for imaging gene effects in ADHD. One structure that has been shown in neuroimaging studies to be structurally different in ADHD is the cerebellum. Based on our findings that (1) cerebellum was the one region that differentiated between probands and their unaffected siblings in terms of size (Durston et al., 2004) and (2) that the effect of DAT1-genotype on activity of the cerebellar vermis was the same for boys with ADHD, their unaffected siblings and controls (Durston et al., 2008), we

hypothesized that this region would be relatively spared from familial effects in ADHD. We speculated that it might be a marker for the disorder itself, rather than for a familial risk. We assessed this in a recent study, where we manipulated the timing of trials in a variation on a go/no-go task (Mulder et al., 2008). Familial effects were investigated in a discordant sibling pair design. We found that both boys with ADHD and their unaffected siblings showed reduced activation in this region in response to timing manipulations. Furthermore, the brothers of boys with ADHD showed reduced performance on trials where timing was manipulated, similar to their affected counterparts. This suggests that cerebellum may still be involved in genetic risk for ADHD. The cerebellum is a large and complex structure with nearly as many neurons as the cerebrum (Williams and Herrup, 1988). It has sufficient complexity to be involved in genetic effects, in addition to showing effects that are specific to the disorder. As such, it may be useful as an endophenotype in studies interested in genes that are expressed in this region.

5.3. Other leads in imaging genetics in ADHD: the serotonin transporter gene

To date, no studies have used neuroimaging to investigate serotonin genes in ADHD. However, effects of a polymorphism in the serotonin transporter gene (5-HTT) have been shown on medial temporal lobe structures in other populations, in particular on the amygdala: the short allele of a polymorphism in the promoter region is associated with greater activation of the amygdala in response to fearful stimuli in healthy adults (Hariri et al., 2002; Smolka et al., 2007) and in anxiety and affective disorders (Dannlowski et al., 2007). This allele has also been shown to affect hippocampal neurochemistry (Gallinat et al., 2005). Furthermore, the 5-HTT gene has been shown to interact with DRD4 genotype to affect anxiety levels in healthy infants (Lakatos et al., 2003). Taken together with the relatively recent implication of medial temporal lobe structures in ADHD (Brieber et al., 2007; Carmona et al., 2005; Castellanos et al., 1996b; Plessen et al., 2006) and the rate of anxiety disorders in these children (Jarrett and Ollendick, 2008), these findings suggest it may be of interest to investigate effects of this polymorphism on the medial temporal lobe in ADHD. Putatively, there could be a shared mechanism between anxiety disorders and ADHD, resulting in an anxious and distractible phenotype or it may even be possible to define a neurobiologically distinct anxious ADHD endophenotype.

A third intriguing new lead for imaging genetics research in ADHD is the overlap between susceptibility for ADHD and substance abuse. A comprehensive discussion of this direction by Jentsch and colleagues is available in this issue of NBR (page 690–698).

6. Conclusion

The first part of this paper reviews the literature on genetics and neuroimaging in ADHD. While data-driven approaches have been successful in suggesting new avenues for research, theory-driven approaches have resulted in the most encouraging findings to date: whole-genome scans have shown few regions of overlap, while candidate gene approaches have suggested several viable candidate genes, including the DRD4 and DAT1 genes. Neuroimaging studies have focused on (aspects of) cognitive control and, as a result, the neurobiological bases of deficits in this ability in ADHD are well understood.

The second part of this paper discusses the literature on imaging genetics in ADHD. Papers to date have taken one of two approaches: the earliest papers investigated the effects of one or two candidate genes on many brain areas, whereas later papers

constrained regions of interest by gene expression patterns. These papers have largely focused on cognitive control and the dopamine circuits involved in this ability. The results show that neuroimaging of cognitive control is useful as an endophenotype in investigating dopamine gene effects in ADHD. New avenues of investigation are suggested by a combination of data- and theory-driven approaches: familial risk for ADHD has been shown to affect activity in the cerebellum, suggesting that this structure may be a future target for studies of genes expressed in this region. The serotonin transporter gene has been implicated in ADHD by both approaches: studies of its effects in other populations suggest that it may relate to findings of smaller medial temporal lobe structures and anxiety in ADHD.

7. Beyond studying the biology of ADHD

Imaging genetics approaches in ADHD have focused on cognitive control and are beginning to show us how risk alleles impact the brain and may ultimately result in symptoms. But will improved neurobiological understanding of these cascades actually benefit individuals with this disorder? We believe that imaging genetics approaches have the potential to reshape the way we think about ADHD: if multiple endophenotypes can be defined that lead to symptoms of ADHD, we will ultimately be able to define subtypes based on their biological signature. For example, studies exploring changes in the cerebellum may find that these changes are specific to a subgroup of individuals with ADHD, who have problems forming temporal expectations about the environment. Clinically, the symptoms resulting from failing to build up such expectations could be similar to those from a breakdown of cognitive control (Nigg and Casey, 2005). However the underlying biological mechanisms could be quite different. Such different biological ADHD-types may have differential responses to treatments. Whereas deficits in cognitive control can be ameliorated by methylphenidate through fronto-striatal functioning (e.g., Vaidya et al., 1998), a more cerebellar form of ADHD may be better treated by substances that target cerebellar neurotransmission directly. As such, defining endophenotypes in ADHD and using them to inform us about the underlying neurobiology has the potential to create a more individually tailored approach treatment approach in ADHD, where appropriate treatments can be chosen based on individual endophenotype profiles. Ultimately, tracking the developmental trajectories of individual ADHD endophenotypes may even point us towards possibilities for early identification of individuals at risk, thereby creating a window for developing preventative strategies.

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