Development and Psychopathology **20** (2008), 1133–1143
Copyright © 2008 Cambridge University Press
Printed in the United States of America
doi:10.1017/S0954579408000539

Converging methods in studying attention-deficit/hyperactivity disorder: What can we learn from neuroimaging and genetics?

SARAH DURSTON
University Medical Center Utrecht and Weill Medical College of Cornell University

Abstract

This paper discusses how converging methods may form a powerful tool in unraveling the neurobiology of attention-deficit/hyperactivity disorder (ADHD). Integrating findings from multiple disciplines can inform us on how different neurobiological and cognitive mechanisms tie together in both typical and atypical development. Examples are discussed of this approach: combining family and genetic approaches with anatomical neuroimaging illustrates how mapping familial effects can bring us closer to understanding the neurobiology of ADHD. Functional neuroimaging has convincingly linked cognitive problems in this disorder with frontostriatal functioning, but also shows that other systems may be involved in some of the symptoms of ADHD. Combining these findings has suggested new avenues for investigation, such as the role of frontocerebellar networks. Furthermore, findings may have practical applications: this paper discusses an example of how converging evidence of striatal dysregulation in ADHD suggests possible directions for treatment that are now being explored in functional imaging studies.

Attention-deficit/hyperactivity disorder (ADHD) is a behaviorally defined neuropsychiatric disorder with onset by age 7. Developmentally inappropriate levels of activity and impulsivity characterize the disorder, as well as disorganized and inattentive behavior (American Psychiatric Association, 2000; Kaplan, Sardock, & Grubb, 1994). Although traditionally ADHD was thought to be outgrown by puberty, more recent perspectives have shifted to viewing it as a chronic developmental disorder, persisting into adulthood in at least 30% of the patients (Wilens et al., 2002).

Nearly all of the theoretical accounts of ADHD address aspects of cognitive control in some form. Cognitive control is characterized as the ability to suppress inappropriate behaviors in response to contextual and temporal cues and adjust behavior accordingly (Nigg & Casey, 2005). Diagnostic criteria for ADHD reflect these deficits, as they include inappropriate and disruptive behaviors in inappropriate contexts, such as blurting out (unintentionally hurtful) comments, disruptive behavior in the classroom, and potentially dangerous behaviors, such as running out into traffic. Although a significant amount of research has now addressed the neurobiological bases of ADHD, the etiological pathways are still not understood. This paper discusses this issue from a converging methods approach. Such approaches are being used more and more to investigate complex psychiatric disorders, as they have the potential to link findings from multiple levels. This approach is in keeping with a "multiple levels of analysis" approach that is being called for in developmental psychopathology

The work described in this paper was in part supported by a Dutch Science Foundation (NWO) VIDI to the author.

Address correspondence and reprint requests to: Sarah Durston, Rudolf Magnus Institute of Neuroscience, Department of Child and Adolescent Psychiatry, Neuroimaging Lab, HP A 01.468, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands; E-mail: S.Durston@umcutrecht.nl.

https://doi.org/10.1017/S0954579408000539 Published online by Cambridge University Press

(see Special Issues of this Journal by Cicchetti & Curtis, 2007; Cicchetti & Dawson, 2002). The aim of this paper is to illustrate how such approaches permit the integration of findings from multiple disciplines, in this case by investigating the relationship between genes, brain, and cognitive development. Given the relevance of cognitive control to ADHD, this paper begins with an overview of the typical development of this ability and relevant brain circuitry. Then it selectively reviews family, genetic, and neuroimaging studies in ADHD to discuss how common and disparate findings may be integrated. Finally, it discusses implications for future translational research.

Typical Development of Cognitive Control and Frontostriatal Systems

Cognitive control has a protracted development, with aspects of this ability not reaching adult levels until late adolescence. By definition, this development coincides with structural brain development. Magnetic resonance imaging (MRI)-based measures show that cortical gray matter first increases in volume, followed by postadolescent decreases (Giedd et al., 1999). Volume loss occurs earliest in primary sensorimotor areas and latest in the dorsolateral prefrontal cortex (PFC; Gogtay et al., 2004). These changes in volume of brain tissue are thought to represent developmental processes such as, synapse formation and myelination (increases in volume), and selective pruning and apoptosis (programmed cell death) that are linked to decreases in volume later in development. Both types of change are critical to healthy brain development. Investigators have linked such neuroanatomical development to cognitive changes. For example, Casey and colleagues (1997) reported associations between MRI-based prefrontal volume and specific measures of cognitive control, where developmental improvements in performance on an attention task were correlated with greater volume of the anterior cingulate gyrus. Studies such as this suggest that, perhaps not surprising, functional changes in brain development are reflected in structural changes.

Functional MRI investigates structure–function relations more directly. Studies using this technique have suggested different developmental trajectories for different brain regions. For example, cross-sectional studies have shown differential recruitment of subcortical as opposed to cortical regions with development: Casey and colleagues (2002) examined the development of neural systems involved in establishing new stimulus–response mappings, while overriding preexisting ones. Here, the extent of activation in subcortical structures (hippocampus for new learning, striatum for overriding old responses) was far greater for children than adults, whereas their performance was significantly worse, suggesting that as these functions mature, the pattern of activation associated with them becomes more focused. This occurred in parallel with greater recruitment of cortical regions with maturation.

In a longitudinal study we tracked the development of cognitive control in a sample of children as they reached adolescence (Durston, Davidson, et al., 2006). We showed a developmental shift in patterns of cortical activation from diffuse to focal activity. Sensorimotor regions uncorrelated with task performance were recruited less, but a region in the ventral PFC, where activation correlated with task performance, showed enhanced recruitment. In contrast, activation in structures such as the primary motor cortex remained unchanged for the simple comparison of responding (go) versus not responding (no-go) during performance of the task.

It is unclear whether such developmental shifts in activation from diffuse to more focal patterns reflect the functional consequences of synaptic pruning, other regressive processes, or strengthening of relevant connections. The development of new imaging techniques, such as diffusion tensor imaging (DTI), is beginning to allow us to assess some of these issues. This technique uses the properties of water diffusion in white matter to assess the integrity of these tracts. Liston and colleagues (2006) used this technique to relate functional development of frontostriatal networks to the changes in the connectivity between these structures. Diffusion in all assessed white matter tracts became more restricted between the ages of 7 and 30 years. This shift was paralleled by an age-associated increase in efficiency in cognitive control. However, changes in myelination of the frontostriatal tract predicted individual differences in task performance, whereas changes in other tracts did not.

https://doi.org/10.1017/S0954579408000539 Published online by Cambridge University Press

These studies illustrate that developmental changes in brain structure and function underlie the development of cognitive control, in particular, in frontostriatal circuits. Understanding the typical developmental trajectories is important for examining developmental disorders, such as ADHD. This is perhaps best illustrated by an example, such as determining whether atypical development in ADHD is due to a developmental delay or deficit. This is a longstanding debate in the ADHD literature: behaviors associated with this disorder may be completely appropriate at one age but inappropriate at another. As such, ADHD may reflect residual processes that do not necessarily diminish or change with maturity. Neurobiological studies to date have not yet been able to clarify this issue, in part as they have not been able to track development within individuals. Shaw and colleagues (2007) recently investigated the developmental trajectory of cortical gray matter in a longitudinal data set including more than 800 MRI scans from close to 450 children with ADHD and controls. They mapped the trajectory of gray matter thickness at more than 40,000 points in the cortex and found that cortical gray matter in ADHD largely followed the same trajectory as in typically developing children, but that it lagged behind by on average 3 years. This constitutes the first neurobiological evidence that ADHD is associated with a developmental lag. Examples such as this illustrate the importance of understanding typical developmental progressions in investigating ADHD and other developmental disorders.

Family and Genetic Studies of ADHD

Twin and adoption studies indicate that ADHD has a strong genetic component, with additive genetic effects explaining up to 80% of the variance in the phenotype (e.g., Albayrak, Friedel, Schimmelmann, Hinney, & Hebebrand, 2008; Thapar, Holmes, Poulton, & Harrington, 1999). The disorder tends to cluster in families, with an increased incidence among first- and second-degree relatives of affected individuals (Faraone et al., 1995). Siblings of children with ADHD have a three- to fivefold increase in the risk of developing disorder (Biederman et al., 1992; Faraone et al., 1993) and the risk is greater for monozygotic twins with 50 to 80% concordance than for dizygotic twins with a 33% rate, similar to full siblings (Bradley & Golden, 2001; Thapar et al., 1999). Of interest, although ADHD clusters in families, ADHD subtypes do not (Smalley et al., 2001). As such, ADHD families can include individuals with differing phenotypes, including both more inattentive and impulsive subtypes. This suggests that there may not be a direct link between risk genes and the clinical phenotype; rather, mediating factors may be involved. In this model, ADHD risk genes may predispose toward ADHD symptoms, but other influences (such as gender, other genes, or environmental factors) are decisive for the form this predisposition ultimately takes in the phenotype.

The search for genes that convey risk for ADHD is ongoing. In a genome scan, all chromosomes are screened for linkage with markers spaced evenly throughout the genome. This approach has the advantage that it does not require an a priori hypothesis of which genes (or regions on the genome) are involved. To date, genome scans in ADHD have been conducted in four independent samples from the United States, The Netherlands, Germany, and a genetically isolated sample from Colombia (Arcos-Burgos et al., 2004; Bakker et al., 2003; Fisher et al., 2002; Hebebrand et al., 2006; Ogdie et al., 2003). These studies have identified a number of possible loci as associated with ADHD with some overlap between them, although there are many more regions that differ between studies (Faraone et al., 2005). Of interest, a region on chromosome 5p13, proximal to the dopamine transporter gene, was found in the Dutch, German, and US samples. The "logarithm of the odds" (LOD score) of linkage, used to express the odds that a marker is associated with a disorder, was >1 in all three samples. This is not a particularly high LOD score (typically, scores >2.2 would be considered suggestive of linkage), but it is the only region to have been replicated in all three samples (Albayrak et al., 2008). 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 design. There are many more candidate gene studies in ADHD than genome scans. A large number of genes have been investigated,

https://doi.org/10.1017/S0954579408000539 Published online by Cambridge University Press

particularly in the catecholamine systems. However, many positive results have failed to replicate. A fairly recent meta-analysis concluded that, to date, only seven candidate genes have risk alleles where the pooled odds ratio is significantly >1.0 and that are therefore overtransmitted in ADHD. These genes include five catecholamine genes (dopamine 4 [*DRD4*] and dopamine 5 [*DRD5*] receptors, dopamine transporter [*DAT1*], dopamine-beta-hydroxylase [*DBH*], and *SNAP-25* genes) and two in the serotonin system (serotonin transporter [*5-HTT*] and serotonin 1B-receptor [*HTR1B*] genes; Faraone et al., 2005). The five catecholamine genes have clear theoretical relevance in ADHD, given the mechanism of action of stimulant medication for ADHD (Biederman & Faraone, 2002). These drugs stimulate release and inhibit reuptake of catecholamines (dopamine and noradrenalin), thus enhancing the activity of these neurotransmitter systems. The effectiveness of these treatments has led to the catecholamine dysregulation hypothesis of ADHD that posits that symptoms are related to a dysregulation of catecholamines, in particular dopamine (for a review, see Pliszka, McCracken, & Maass, 1996). According to this hypothesis, cognitive impairments associated with ADHD result from a hypodopaminergic state in the PFC, whereas hyperactivity and impulsivity result from a hyperdopaminergic state in striatum, possibly secondary to the prefrontal hypodopaminergic state (Solanto, 2002). Here, prefrontal inhibition of striatum is hypothesized to be disrupted by the hypodopaminergic state in the PFC. Because the PFC projects to many subcortical regions, including the dorsal and ventral striatum, thalamus, amygdala, substantia nigra, and ventral tegmental area (Alexander, DeLong, & Strick, 1986), PFC dysfunction may also lead to disinhibition of these regions. Stimulants may then act by increasing prefrontal dopaminergic neurotransmission, resulting in improvement in both cognitive functioning and behavioral symptoms.

The variation in the *DRD4* gene may be associated with postsynaptic receptor subsensitivity to dopamine, thus mediating a blunted response to the transmitter (Asghari et al., 1995). The variation in the *DAT1* gene may be associated with change in dopamine transporter activity, where it becomes overly efficient at the reuptake process. Both may lead to underactivity in dopamine pathways (Swanson & Castellanos, 1998; Swanson et al., 2000; Swanson & Volkow, 2002). Little is yet known about the functional relevance of allelic variants in the *DRD5* gene, although it has been suggested that they may be involved efficiency of gene transcription (Albayrak et al., 2008). DBH is an enzyme responsible for the conversion of dopamine into noradrenalin. Polymorphisms in the *DBH* gene may affect the function of gene products or modify gene expression and thus influence the progression of ADHD (Paclt et al., 2005). *SNAP-25* has been implicated in the etiology of ADHD based on the mouse mutant strain Coloboma (Wilson, 2000). Mutations within the gene are thought to affect the release of dopamine (as well as other neurotransmitters), thereby altering the ratio of noradrenalin to dopamine (Kirley et al., 2002).

The serotonin system has some theoretical relevance to ADHD, given its implication in impulsivity, aggression, and disinhibited behavior in both animal and human studies. Polymorphisms in the serotonin transporter (*5-HTT*) gene may result in reduced transcription and lower transporter protein levels. Similarly, a mutation in the *HTR1B* gene, which encodes the 5HT1B receptor, may lead to a decrease in serotonin activity (Hawi et al., 2002).

In sum, family studies indicate that ADHD is heritable, but there is no obvious link between risk genes and the clinical phenotype. To date, genome scans have been conducted in four independent samples. Although there is some overlap, there are many more differences between these studies. Candidate gene studies are grounded in theoretical constructs of ADHD, and have provided confirmation of catecholamine involvement in the disorder, as well as some evidence for serotonin involvement. Given the evidence for relatively high heritability of the disorder, it is surprising that the involvement of only few genes has yet been tentatively confirmed. This may be because a clinical diagnosis such as ADHD does not map onto the neurobiological effects of gene variations. The use of intermediate or endophenotypes may help us investigate gene effects in ADHD: these phenotypes are intermediate between a clinical diagnosis (such as

https://doi.org/10.1017/S0954579408000539 Published online by Cambridge University Press

ADHD) and the biological variables that are the cause of the disorder (e.g., a risk gene). As they are closer to the biology, they may map onto genetic variation underlying ADHD more closely (Castellanos & Tannock, 2002). A number of theorists have outlined criteria that endophenotypes should meet in order to be beneficial in the study of causative agents in psychiatry, such as being stable, being found in the unaffected family members of affected individuals, and being grounded in neuroscience (Almasy & Blangero, 2001; Castellanos & Tannock, 2002; Gottesman & Gould, 2003). Examples of endophenotypes in ADHD could be aspects of executive functioning or changes in brain structure and functioning: aspects of executive functioning have been shown to cluster in sibling pairs affected with ADHD, suggesting that this may define a more homogeneous subgroup (Slaats-Willemse, Swaab-Barneveld, de Sonneville, van der Muelen, & Burlelaar, 2005). Furthermore, aspects of brain changes in ADHD have been found in the unaffected siblings of affected individuals, suggesting that risk genes may lead to neurobiological changes even without associated changes in behavior (i.e., ADHD symptoms; Durston et al., 2005, Durston, Mulder, et al., 2006; Mulder et al., 2008). As such, neuroimaging measures may provide a noninvasive means of assessing neurobiological changes in ADHD that are more closely tied to genetic variation in this disorder than clinical measures. A more detailed discussion of using MR measures in an endophenotype approach to ADHD follows below.

Mapping Family and Genetic Effects on the Brain in ADHD

The most reliable finding from anatomical MRI studies of individuals with ADHD is probably a subtle reduction in total brain volume, compared to typically developing children. In addition to this global reduction in volume, three regional findings are notable: relative to controls, individuals with ADHD show (a) smaller MRI-based volumes of the caudate nucleus, (b) smaller prefrontal volumes, and (c) differences in the cerebellum, in particular, a smaller vermis (e.g., Castellanos et al., 2002; Shaw et al., 2006). These findings tie in with theoretical accounts of ADHD that often stress the involvement of cognitive control in this disorder (Barkley, 1997; Casey & Durston, 2006). As described above, cognitive control and the development of this ability rely on intact frontostriatal circuitry.

As neuroimaging can be used to assess neurobiological changes that may be more closely tied to genetic variation, investigators have begun to study brain changes in family members of affected individuals. For example, we showed that reductions in cortical gray matter were present in siblings with and without ADHD (Durston et al., 2004). Furthermore, we showed that two ADHD risk genes directly impacted frontostriatal gray matter volumes (Durston et al., 2005). Both the *DRD4* and *DAT1* genes are of theoretical relevance in ADHD, and both have been associated with the disorder in multiple studies. In our study, allele-specific effects were consistent with gene-expression patterns in the brain: the DRD4 genotype was associated with a reduction in prefrontal gray matter volume, and the DAT1 genotype was associated with reduced caudate nucleus volume (Durston et al., 2005). This example illustrates how we can begin to map the effects of ADHD risk genes on neurobiological measures, both indirectly (effects are shared by family members who may be carriers of unknown risk genes) and directly (defined ADHD risk genes can be shown to affect brain structure). However, these studies are perhaps most informative when we can begin to show how gene effects are involved in translating genetic risk into neurobiology: in a recent functional imaging study, we were able to show differential effects of the DAT1 genotype on brain activation patterns between individuals at genetic risk for ADHD and controls. We found that the DAT1 genotype interacted with familial risk for ADHD in the striatum, but not in the vermis of the cerebellum. In the striatum, the effect of the DAT1 risk allele was specific to those individuals at familial risk for the disorder (affected and unaffected siblings). For controls, activity in this region was not different between carriers and noncarriers of the variant allele (Durston, Fossella, et al., 2008). In the vermis the effect of DAT1 genotype was the same in all three groups. This suggests that the *DAT1* gene effects in the striatum may be involved in translating a genetic risk for ADHD into a neurobiological substrate, as they were only found for individuals

https://doi.org/10.1017/S0954579408000539 Published online by Cambridge University Press

who were at familial risk for ADHD (boys with ADHD and their unaffected siblings). These results are best considered in the context of a broader program of research investigating the effects of familial risk and risk genes for ADHD on brain structure and function. Familial effects and the effects of ADHD risk genes appear to be most obvious in prefrontal and striatal areas (Durston et al., 2004, 2005, Durston, Mulder, et al., 2006, 2008). In our initial report, we found that cerebellum was the only region to differentiate between siblings with and without ADHD, as its volume was reduced in affected but not unaffected siblings (Durston et al., 2004). Taken together with the current finding that the DAT1 genotype interacts with familial risk for ADHD in the striatum, but not the cerebellar vermis, this suggests that the cerebellum may be relatively spared from familial effects in ADHD. However, in a recent report where cerebellar activity was specifically targeted, we did find effects of familial risk in this region (Mulder et al., 2008). This suggests that although effects of familial risk and dopamine genes may be most obvious in frontostriatal circuits, they do play a part in other regions of the brain. By using tasks that specifically target different regions, we are beginning to address these different influences (for review, see Durston, de Zeeuw, & Staal, in press).

Functional Neuroimaging Approaches to Understanding ADHD

Functional neuroimaging techniques are increasingly being used to investigate brain activation patterns in ADHD in response to cognitive demands. Tasks that tax cognitive control in some way are frequently used, given that problems in this ability are well established in ADHD (Barkley, 1997). These studies have shown that differences in cognitive control between subjects with and without ADHD are associated with differences in brain activation patterns (e.g., Bush et al., 1999; Durston et al., 2003; 2006; Konrad et al., 2006; Rubia et al., 1999; Vaidya et al., 1998). In particular, they have demonstrated reduced activation in prefrontal and striatal regions during paradigms that require subjects to suppress prepotent tendencies as part of the task, such as go/no-go or Stroop paradigms (Booth et al., 2005; Bush et al., 1999; Durston et al., 2003, Durston, Mulder, et al., 2006; Konrad et al., 2006; Pliszka et al., 2006; Rubia et al., 1999; Rubia, Smith, Brammer, Toone, & Taler, 2005; Schulz et al., 2004; Schulz, Newcorn, Fan, Tang, & Halpern, 2005; Schulz, Tang, et al., 2005; Shafritz, Marchione, Gore, Shaywitz, & Shaywitz, 2004; Smith, Taylor, Brammer, Toone, & Rubia, 2006; Suskauer et al., 2007; Tamm, Menon, Ringel, & Reiss, 2004; Vaidya et al., 1998, 2005; Zang et al., 2005). In go/no-go tasks, subjects are required to respond to a stream of predictable stimuli with a button press. In the case of a rare no-go stimulus, they are to suppress this response. We used a version of this paradigm to show reduced frontostriatal activation for children with ADHD compared to controls, even when performance was similar (Durston et al., 2003). In the classic Stroop paradigm, subjects are required to name the color of ink in which a color-word is printed, while suppressing the automatic tendency to read the word instead. For example, the word "blue" printed in red ink should elicit the response "'red." Several variations on this classic task have been developed, including a counting stroop, where subjects are required to count the number of times a word appears on a screen, regardless of word meaning (Bush et al., 1999). For example, the correct response to four appearances of the word "one" would be "four." Bush et al. (1999) used this paradigm to show reduced activation of anterior cingulate gyrus in ADHD. The pattern of decreased activation in prefrontal and striatal areas in cognitive control tasks has led investigators to suggest that deficits in these regions may be central to ADHD (for a review, see Bush, Valera, & Seidman, 2005; Durston, 2003). Other studies have used paradigms that investigate other aspects of behavior, such as aspects of attention (Bush et al., 2008; Konrad, Neufang, Hanisch, Fink, & Herpertz-Dhalmann, 2006; Konrad, Neufang, Fink, & Herpertz-Dahlmann, 2007; Shafritz et al., 2004; Stevens, Peralson, & Kiehl, 2007; Tamm, Menon, & Reiss, 2006), mental rotation paradigms (Silk et al., 2005) and motivated behavior (Scheres, Miham, Knutson, & Castellanos, 2007; Ströhle et al., 2008). Again, deficits in striatal (Konrad et al., 2006; Shafritz et al., 2004; Silk et al., 2005; Scheres et al., 2007; Ströhle et al., 2008) and prefrontal (Konrad et al., 2006; Silk et al., 2005) activation have been

https://doi.org/10.1017/S0954579408000539 Published online by Cambridge University Press

found, as well as changes in activation in parietal areas (Konrad et al., 2006; Shafritz et al., 2004; Silk et al., 2005; Stevens et al., 2007). These findings underscore the importance of frontostriatal networks in ADHD, as deficits in this network have now been associated with a wide range of cognitive tasks. One question that remains unanswered is how changes in frontostriatal functioning and associated cognitive deficits are related to anatomical changes. A recent study used DTI to show that reduced frontostriatal activation during a go/no-go task was related to reduced white matter integrity in both children with ADHD and their affected parents (Casey, Epstein, et al., 2007). This suggests that disruption of frontostriatal white matter tracts may contribute to a familial form of the disorder.

Converging Methods Suggest New Directions in ADHD Research

Both anatomical and functional MR studies of ADHD show changes in frontostriatal circuitry. This ties in with theoretical accounts of ADHD that stress the relevance of cognitive control in this disorder. However, recent work is suggesting new directions in investigating the neurobiological etiology in ADHD, as well as new possible directions for treatment. Two examples are discussed below.

Frontocerebellar loops in the etiology of ADHD

The only study to date to investigate neural functioning in a noncognitive task did not show frontostriatal changes: Mostofsky and colleagues (2006) investigated neural correlates of simple motor movements in ADHD and reported reduced activation in parietal and primary motor cortex only. These findings could be interpreted as suggesting that frontostriatal involvement is more specific to the cognitive and motivational deficits associated with ADHD, whereas motor clumsiness in this disorder may have a different neurobiological basis. Alternatively, there may be a different neurobiological deficit contributing to both types of symptoms in ADHD: cognitive control is dependent on the ability to predict temporal and contextual structure in the environment (Nigg & Casey, 2005). Knowing *what* to expect and *when* to expect it is critical in planning and maintaining appropriate thoughts and actions over time. If basic expectations about the environment are inaccurate or less salient for children with ADHD, then their ability to detect *violations* of expectation will be compromised, and their ability to adjust their behavior accordingly will be weakened (Nigg & Casey, 2005). Specifically, if children with ADHD have trouble predicting the occurrence of events accurately, their reaction to a predictable event should be (a) slower and (b) more variable. We tested this in two independent samples of children and adolescents with ADHD. We found that they were not able to benefit behaviorally from trials being predictable to the same degree as control subjects (Durston et al., 2007). We used a variation of a go/no-go task, where the predictability of events was manipulated in two ways: expected or unexpected stimuli (go and no/go) were presented at expected or unexpected times. Behaviorally, children and adolescents with ADHD had increased variability in reaction times, and decreased benefit in reaction time when events were predictable. Differences in accuracy between groups were most reliable for temporally unpredictable trials. Furthermore, these behavioral changes were accompanied by decreases in frontostriatal and cerebellar activation. Prefrontal areas were most affected on unpredictable trials where stimulus identity was violated, whereas the cerebellum was most affected when timing was violated. These findings are consistent with the view that disruptive behaviors in inappropriate contexts, a major criterion in diagnosing ADHD, may be related to an impaired ability to predict temporal and contextual cues in the environment, thus hindering the ability to alter behavior when they change. Furthermore, they could be related to motor deficits in ADHD, if structure and timing of self-paced behaviors is similarly affected. Different processes may be involved in ADHD in different individuals.

A role for striatal reward circuitry in treating ADHD?

Identification of which cognitive and neural processes are involved and recognizing different

https://doi.org/10.1017/S0954579408000539 Published online by Cambridge University Press

biological causes may permit more individualized, biologically targeted interventions and treatments (Casey, Nigg, & Durston, 2007). Recently, two functional imaging studies showed reduced activation in ventral striatum in ADHD on tasks where subjects anticipated reward (Scheres et al., 2007; Ströhle et al., 2008), in addition to striatal dysregulation in cognitive control tasks. Such converging evidence of dopamine dysregulation in striatum suggests new directions for intervention, where it may be possible to improve cognitive control in ADHD by using reward strategies. Neuroanatomical studies provide a biological basis for this hypothesis: ventral frontostriatal circuits involved in reward processing project to more dorsolateral networks through spiralling striatonigrostriatal projections (Haber, 2003; Haber, Ki-Sok, Mailly, & Calzavara, 2006). As such, reward may enhance activation in ventral striatum, boosting more dorsolateral networks and lead to improvements in cognitive performance. We recently addressed this in a study directly investigating the effect of reward on cognitive control in ADHD. Reward was parametrically manipulated in the context of a go/no-go task: we manipulated the amount of attainable reward systematically for both go and no-go trials and investigated its effects in two independent samples of children and adolescents with ADHD and controls. In both samples, performance on go trials improved with reward for individuals with and without ADHD, suggesting that the reward manipulation was successful. However, we found no evidence that reward improved cognitive control or activation in frontostriatal circuits (Baeyens et al., 2008): there was no behavioral improvement on no-go trials in either sample, nor was there an effect on fMRI signal on no-go trials (investigated in only one sample). This seems surprising given reports of cognitive improvements with reward in ADHD (for a review, see Luman, Costerlaan, & Sargeant, 2005). However, in our study reward was not specific to those trials requiring cognitive control, nor was it unpredictable: Every trial held the potential of reward. As such, these findings suggest that behavioral programs using small, predictable rewards are likely to be of limited utility in ADHD. However, other strategies using larger or unexpected rewards may still be of use: such unexpected salient events may be able to "jump start" the dopamine bottom-up alerting system in ADHD, rather than "bypassing" it (Casey, Nigg, & Durston 2007).

Implications for Future Studies

This paper discusses examples that show how converging methods may form a powerful tool in unraveling the neurobiology of ADHD. Family and genetic studies stress the relatively high heritability of ADHD and the importance of catecholamine systems in this disorder. Anatomical studies confirm the involvement of frontostriatal circuits and illustrate how mapping familial effects can bring us closer to the neurobiology of ADHD. Functional neuroimaging can begin to link brain changes to behavior and shows how cognitive problems in this disorder are related frontostriatal functioning. By integrating findings from multiple disciplines, we can deduce how different neurobiological and cognitive mechanisms tie together in both typical and atypical development. The approach taken is one of converging methods, coming together to target a single problem in neuroscience. Similar convergence has been called for in developmental psychopathology, where authors are suggesting multiple levels of analysis. Combining different approaches in such a way can suggest new avenues for investigation, as in the example of frontocerebellar networks. Furthermore, findings may have practical applications: this paper discusses an example of how converging evidence of striatal dysregulation in ADHD suggests directions for treatment that are now being explored in functional imaging studies.

References

Albayrak, O., Friedel, S., Schimmelmann, B. G., Hinney, A., & Hebebrand, J. (2008). Genetic aspects in attention-deficit/hyperactivity disorder. *Journal of Neural Transmission*, *115*, 305–315.

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Reviews in Neuroscience*, *9*, 357–381.

https://doi.org/10.1017/S0954579408000539 Published online by Cambridge University Press

Almasy, L., & Blangero, J. (2001). Endophenotypes as quantitative risk factors for psychiatric disease: Rationale and study design. *American Journal of Medical Genetics*, *105*, 42–44.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text revision). Washington, DC: Author.

Arcos-Burgos, M., Castellanos, F. X., Pineda, D., Lopera, F., Palacio, J. D., Palacio, L. G., et al. (2004). Attention-deficit/hyperactivity disorder in a population isolate: Linkage to loci at 4q13.2, 5q33.3, 11q22, and 17p11. *American Journal of Human Genetics*, *75*, 998–1014.

Asghari, V., Sanyal, S., Buchwaldt, S., Paterson, A., Jovanovic, V., & Van Tol, H. H. (1995). Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. *Journal of Neurochemistry*, *65*, 1157–1165.

Baeyens, D., Mulder, M. J., Roeyers, H., Verbeke, T., Froninckx, K., van Engeland, H., et al. (2008). *Does reward affect cognitive control in ADHD: An fMRI study*. Manuscript submitted for publication.

Bakker, S. C., van der Meulen, E. M., Buitelaar, J. K., Sandkuijl, L. A., Pauls, D. L., Monsuur, A. J., et al. (2003). A whole-genome scan in 164 Dutch sib pairs with attention-deficit/hyperactivity disorder: Suggestive evidence for linkage on chromosomes 7p and 15q. *American Journal of Human Genetics*, *72*, 1251–1260.

Bakker, S. C., van der Meulen, E. M., Buitelaar, J. K., Sandkuijl, L. A., Pauls, D. L., Monsuur, A. J., et al. (2005). DAT1, DRD4, and DRD5 polymorphisms are not associated with ADHD in Dutch families. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *132*, 50–52.

Barkley, R. A. (1997). Behavioral inhibition, sustained attention and executive functions, constructing a unifying theory of ADHD. *Psychological Bulletin*, *21*, 65–94.

Biederman, J., & Faraone, S. V. (2002). Current concepts on the neurobiology of attention-deficit/hyperactivity disorder. *Journal of Attention Disorders*, *6*(Suppl. 1), S7–S16.

Biederman, J., Faraone, S. V., Keenan, K., Benjamin, J., Krifcher, B., Moore, C., et al. (1992). Further evidence for family-genetic risk factors in attention deficit hyperactivity disorder. Patterns of comorbidity in probands and relatives in psychiatrically and pediatrically referred samples. *Archives of General Psychiatry*, *49*, 728–738.

Booth, J. R., Burman, D. D., Meyer, J. R., Lei, Z., Trommer, B. L., Davenport, N. D., et al. (2005). Larger deficits in brain networks for response inhibition than for visual selective attention in attention deficit hyperactivity disorder (ADHD). *Journal of Child Psychology and Psychiatry*, *46*, 94–111.

Bradley, J. D., & Golden, C. J. (2001). Biological contributions to the presentation and understanding of attention-deficit/hyperactivity disorder, a review. *Clinical Psychology Review*, *21*, 907–929.

Bush, G., Frazier, J. A., Rauch, S. L., Seidman, L. J., Whalen, P. J., Jenike, M. A., et al. (1999). Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the counting Stroop. *Biological Psychiatry*, *45*, 1542–1552.

Bush, G., Spencer, T. J., Holmes, J., Shin, L. M., Valera, E. M., Seidman, L. J., et al. (2008). Functional magnetic resonance imaging of methylphenidate and placebo in attention-deficit/hyperactivity disorder during the multi-source interference task. *Archives of General Psychiatry*, *65*, 102–114.

Bush, G., Valera, E. M., & Seidman, L. J. (2005). Functional neuroimaging of attention-deficit/hyperactivity disorder, a review and suggested future directions. *Biological Psychiatry*, *57*, 1273–1284.

Casey, B. J., & Durston, S. (2006). From behavior to cognition to the brain and back: What have we learned from functional imaging studies of attention deficit hyperactivity disorder? *American Journal of Psychiatry*, *163*, 957–960.

Casey, B. J., Epstein, J. N., Buhle, J., Liston, C., Davidson, M. C., Tonev, S. T., et al. (2007). Frontostriatal connectivity and its role in cognitive control in parent–child dyads with ADHD. *American Journal of Psychiatry*, *164*, 1729–1736.

Casey, B. J., Nigg, J., & Durston, S. (2007). Behavioral, imaging and genetic studies suggest new directions in treatment of attention deficit hyperactivity disorder. *Current Opinion in Neurology*, *20*, 119–124.

Casey, B. J., Thomas, K. M., Davidson, M. C., Kunz, K., & Franzen, P. L. (2002). Dissociating striatal and hippocampal function developmentally with a stimulus–response compatibility task. *Journal of Neuroscience*, *22*, 8647–8652.

Casey, B. J., Trainor, R. J., Orendi, J. L., Schubert, A. B., Nystrom, L. E., Giedd, J. N., et al. (1997). A developmental functional MRI study of prefrontal activation during performance of a go-nogo task. *Journal of Cognitive Neuroscience*, *9*, 835–847.

Castellanos, F. X., Lee, P. P., Sharp, W., Jeffries, N. O., Greenstein, D. K., Clasen, L. S., et al. (2002). Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Medical Association*, *288*, 1740–1748.

Castellanos, F. X., & Tannock, R. (2002). Neuroscience of attention-deficit/hyperactivity disorder, the search for endophenotypes. *Nature Review Neuroscience*, *3*, 617–628.

Cicchetti, D., & Curtis, W. J. (Eds.). (2007). A multilevel approach to resilience. *Development and Psychopathology*, *19*, 627–955.

Cicchetti, D., & Dawson, G. (Eds.). (2002). Multiple levels of analysis. *Development and Psychopathology*, *14*, 417–666.

Durston, S. (2003). A review of the biological bases of ADHD, what have we learned from imaging studies? *Mental Retardation and Developmental Disabilities Research Reviews*, *9*, 184–195.

Durston, S., Davidson, M. C., Mulder, M. J., Spicer, J. A., Galvan, A., Tottenham, N., et al. (2007). Neural and behavioral correlates of expectancy violations in attention-deficit hyperactivity disorder. *Journal of Child Psychology and Psychiatry*, *48*, 881–889.

Durston, S., Davidson, M. C., Tottenham, N., Galvan, A., Spicer, J., Fossella, J. A., et al. (2006). A shift from diffuse to focal cortical activity with development. *Developmental Science*, *9*, 1–8.

Durston, S., de Zeeuw, P., & Staal, W. (in press). Imaging genetics in ADHD: A focus on cognitive control. *Neuroscience & Biobehavioral Reviews*.

Durston, S., Fossella, J. A., Casey, B. J., Hulshoff Pol, H. E., Galvan, A., Schnack, H. G., et al. (2005). Differential effects of DRD4 and DAT1 genotype on fronto-striatal gray matter volumes in a sample of subjects with attention deficit hyperactivity disorder, their unaffected siblings, and controls. *Molecular Psychiatry*, *10*, 678–685.

https://doi.org/10.1017/S0954579408000539 Published online by Cambridge University Press

Durston, S., Fossella, J. A., Mulder, M. J., Casey, B. J., Ziermans, T. B., Vessaz, M. N., et al. (2008). Dopamine-transporter genotype conveys familial risk for attention-deficit/hyperactivity disorder through striatal activation. *Journal of the American Academy of Child & Adolescent Psychiatry*, *47*, 61–67.

Durston, S., Hulshoff Pol, H. E., Schnack, H. G., Buitelaar, J. K., Steenhuis, M. P., Minderaa, R. B., et al. (2004). Magnetic resonance imaging of boys with attention deficit hyperactivity disorder and their unaffected siblings. *Journal of the American Academy of Child & Adolescent Psychiatry*, *43*, 332–340.

Durston, S., Mulder, M., Casey, B. J., Ziermans, T., & van Engeland, H. (2006). Activation in ventral prefrontal cortex is sensitive to genetic vulnerability for attention-deficit hyperactivity disorder. *Biological Psychiatry*, *60*, 1062–1070.

Durston, S., Tottenham, N. T., Thomas, K. M., Davidson, M. C., Eigsti, I. M., Yang, Y., et al. (2003). Differential patterns of striatal activation in young children with and without ADHD. *Biological Psychiatry*, *53*, 871–878.

Faraone, S. V., Biederman, J., Chen, W. J., Milberger, S., Warburton, R., & Tsuang, M. T. (1995). Genetic heterogeneity in attention-deficit hyperactivity disorder (ADHD), gender, psychiatric comorbidity, and maternal ADHD. *Journal of Abnormal Psychology*, *104*, 334–345.

Faraone, S. V., Biederman, J., Lehman, B. K., Keenan, K., Norman, D., Seidman, L. J., et al. (1993). Evidence for independent transmission in families for attention deficit hyperactivity disorder (ADHD) and learning disability, results from a family genetic study of ADHD. *American Journal of Psychiatry*, *150*, 891–895.

Faraone, S. V., Perlis, R. H., Doyle, A. E., Smoller, J. W., Goralnick, J. J., Holmgren, M. A., et al. (2005). Molecular genetics of attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *57*, 1313–1323.

Fisher, S. E., Francks, C., McCracken, J. T., McGough, J. J., Marlow, A. J., MacPhie, I. L., et al. (2002). A genomewide scan for loci involved in attention-deficit/hyperactivity disorder. *American Journal of Human Genetics*, *70*, 1183–1196.

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Lui, H., Zijdenbos, A., et al. (1999). Brain development during childhood and adolescence: A longitudinal MRI study. *Nature Neuroscience*, *10*, 861–863.

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., et al. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences of the United States of America*, *101*, 8174–8179.

Gottesman, I. I., & Gould, T. D. (2003). The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry*, *160*, 636–645.

Haber, S. N. (2003). The primate basal ganglia, parallel and integrative networks. *Journal of Chemical Neuroanatomy*, *26*, 317–330.

Haber, S. N., Ki-Sok, K., Mailly, P., & Calzavara, R. (2006). Reward-related cortical inputs define a large striatal region in primates that interface with associative cortical connections, providing a substrate for incentive-based learning. *Journal of Neuroscience*, *26*, 8368–8376.

Hawi, Z., Dring, M., Kirley, A., Foley, D., Kent, L., Craddock, N., et al. (2002). Serotonergic system and attention deficit hyperactivity disorder (ADHD): A potential susceptibility locus at the *5-HT(1B)* receptor gene in 273 nuclear families from a multi-centre sample. *Molecular Psychiatry*, *7*, 718–725.

Hebebrand, J., Dempfle, A., Saar, K., Thiele, H., Herpertz-Dahlmann, B., Linder, M., et al. (2006). A genome-wide scan for attention-deficit/hyperactivity disorder in 155 German sib-pairs. *Molecular Psychiatry*, *11*, 196–205.

Kaplan, H. I., Sadock, B. J., & Grebb, J. A. (1994). Attention-deficit disorders. In *Kaplan and Sadock's synopsis of psychiatry* (pp. 1063–1068). Baltimore, MD: Williams & Wilkins.

Kirley, A., Hawi, Z., Daly, G., McCarron, M., Mullins, C., Millar, N., et al. (2002). Dopaminergic system genes in ADHD: Toward a biological hypothesis. *Neuropsychopharmacology*, *27*, 607–619.

Konrad, K., Neufang, S., Fink, G. R., & Herpertz-Dahlmann, B. (2007). Long-term effects of methylphenidate on neural networks associated with executive attention in children with ADHD, results from a longitudinal functional MRI study. *Journal of the American Academy of Child & Adolescent Psychiatry*, *46*, 1633–1641.

Konrad, K., Neufang, S., Hanisch, C., Fink, G. R., & Herpertz-Dahlmann, B. (2006). Dysfunctional attentional networks in children with attention deficit/hyperactivity disorder, evidence from an event-related functional magnetic resonance imaging study. *Biological Psychiatry*, *59*, 643–651.

Liston, C., Watts, R., Tottenham, N., Davidson, M. C., Niogi, S., Ulug, A. M., et al. (2006). Frontostriatal microstructure predicts individual differences in cognitive control. *Cerebral Cortex*, *16*, 553–560.

Luman, M., Oosterlaan, J., & Sergeant, S. A. (2005). The impact of reinforcement contingencies on AD/HD: A review and theoretical appraisal. *Clinical Psychology Review*, *25*, 183–213.

Mostofsky, S. H., Rimrodt, S. L., Schafer, J. G., Boyce, A., Goldberg, M. C., Pekar, J. J., et al. (2006). Atypical motor and sensory cortex activation in attention-deficit/hyperactivity disorder, a functional magnetic resonance imaging study of simple sequential finger tapping. *Biological Psychiatry*, *59*, 48–56.

Mulder, M. J., Baeyens, D., Davidson, M. C., Casey, B. J., van den Ban, E., van Engeland, H., et al. (2008). Familial vulnerability to ADHD affects activity in the cerebellum in addition to the prefrontal systems. *Journal of the American Academy of Child & Adolescent Psychiatry*, *47*, 68–75.

Nigg, J. T., & Casey, B. J. (2005). An integrative theory of attention-deficit/hyperactivity disorder based on the cognitive and affective neurosciences. *Developmental Psychopathology*, *17*, 785–806.

Ogdie, M. N., Macphie, I. L., Minassian, S. L., Yang, M., Fisher, S. E., Francks, C., et al. (2003). A genomewide scan for attention-deficit/hyperactivity disorder in an extended sample: Suggestive linkage on 17p11. *American Journal of Human Genetics*, *72*, 1268–1279.

Paclt, I., Koudelova, J., Krepelova, A., Uhlikova, P., Gazdikova, M., & Bauer, P. (2005). Biochemical markers and genetic research of ADHD. *Neuroendocrinology Letters*, *26*, 423–430.

Pliszka, S. R., McCracken, J. T., & Maas, J. W. (1996). Catecholamines in attention-deficit hyperactivity disorder, current perspectives. *Journal of the American Academy of Child & Adolescent Psychiatry*, *35*, 264–272.

Pliszka, S. R., Glahn, D. C., Semrud-Clikeman, M., Franklin, C., Perez, R., III, Xiong, J., et al. (2006). Neuroimaging of inhibitory control areas in children with attention deficit hyperactivity disorder who were treatment naive or in long-term treatment. *American Journal of Psychiatry*, *163*, 1052–1060.

https://doi.org/10.1017/S0954579408000539 Published online by Cambridge University Press

Rubia, K., Overmeyer, S., Taylor, E., Brammer, M., Williams, S. C., Simmons, A., et al. (1999). Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control, a study with functional MRI. *American Journal of Psychiatry*, *156*, 891–896.

Rubia, K., Smith, A. B., Brammer, M. J., Toone, B., & Taylor, E. (2005). Abnormal brain activation during inhibition and error detection in medication-naive adolescents with ADHD. *American Journal of Psychiatry*, *162*, 1067–1075.

Scheres, A., Milham, M. P., Knutson, B., & Castellanos, F. X. (2007). Ventral striatal hyporesponsiveness during reward anticipation in attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *61*, 720–724.

Schulz, K. P., Fan, J., Tang, C. Y., Newcorn, J. H., Buchsbaum, M. S., Cheung, A. M., et al. (2004). Response inhibition in adolescents diagnosed with attention deficit hyperactivity disorder during childhood, an event-related FMRI study. *American Journal of Psychiatry*, *161*, 1650–1657.

Schulz, K. P., Newcorn, J. H., Fan, J., Tang, C. Y., & Halperin, J. M. (2005). Brain activation gradients in ventrolateral prefrontal cortex related to persistence of ADHD in adolescent boys. *Journal of the American Academy of Child & Adolescent Psychiatry*, *44*, 47–54.

Schulz, K. P., Tang, C. Y., Fan, J., Marks, D. J., Newcorn, J. H., Cheung, A. M., et al. (2005) Differential prefrontal cortex activation during inhibitory control in adolescents with and without childhood attention-deficit/hyperactivity disorder. *Neuropsychology*, *19*, 390–402.

Shafritz, K. M., Marchione, K. E., Gore, J. C., Shaywitz, S. E., & Shaywitz, B. A. (2004) The effects of methylphenidate on neural systems of attention in attention deficit hyperactivity disorder. *American Journal of Psychiatry*, *161*, 1990–1997.

Shaw, P., Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J. P., Greenstein, D., et al. (2007). Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proceedings of the National Academy of Sciences of the United States of America*, *104*, 19649–19654.

Shaw, P., Lerch, J., Greenstein, D., Sharp, W., Clasen, L., Evans, A., et al. (2006). Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, *63*, 540–549.

Silk, T., Vance, A., Rinehart, N., Egan, G., O'Boyle, M., Bradshaw, J. L., et al. (2005). Fronto-parietal activation in attention-deficit hyperactivity disorder, combined type: Functional magnetic resonance imaging study. *British Journal of Psychiatry*, *187*, 282–283.

Slaats-Willemse, D., Swaab-Barneveld, H., de Sonneville, L., van der Meulen, E., & Buitelaar, J. K. (2003). Deficient response inhibition as a cognitive endophenotype of ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry*, *42*, 1242–1248.

Smalley, S. L., McCracken, J., & McGough, J. (2001). Refining the ADHD phenotype using affected sibling pair families. *American Journal of Medical Genetics*, *105*, 31–33.

Smith, A. B., Taylor, E., Brammer, M., Toone, B., & Rubia, K. (2006). Task-specific hypoactivation in prefrontal and temporoparietal brain regions during motor inhibition and task switching in medication-naive children and adolescents with attention deficit hyperactivity disorder. *American Journal of Psychiatry*, *163*, 1044–1051.

Solanto, M. V. (2002). Dopamine dysfunction in AD/HD, integrating clinical and basic neuroscience research. *Behavioral Brain Research*, *130*, 65–71.

Stevens, M. C., Pearlson, G. D., & Kiehl, K. A. (2007). An FMRI auditory oddball study of combined-subtype attention deficit hyperactivity disorder. *American Journal of Psychiatry*, *164*, 1737–1749.

Ströhle, A., Stoy, M., Wrase, J., Schwarzer, S., Schlagenhauf, F., Huss, M., et al. (2008). Reward anticipation and outcomes in adult males with attention-deficit/hyperactivity disorder. *NeuroImage*, *39*, 966–972.

Suskauer, S. J., Simmonds, D. J., Fotedar, S., Blankner, J. G., Pekar, J. J., Denckla, M. B., et al. (2007). Functional magnetic resonance imaging evidence for abnormalities in response selection in attention deficit hyperactivity disorder: Differences in activation associated with response inhibition but not habitual motor response. *Journal of Cognitive Neuroscience*, *20*, 478–493.

Swanson, J. M., & Volkow, N. D. (2002). Pharmacokinetic and pharmacodynamic properties of stimulants: Implications for the design of new treatments for ADHD. *Behavioural Brain Research*, *130*, 73–78.

Swanson, J., Castellanos, F. X., Murias, M., LaHoste, G., & Kennedy, J. (1998). Cognitive neuroscience of attention deficit hyperactivity disorder and hyperkinetic disorder. *Current Opinion in Neurobiology*, *8*, 263–271.

Swanson, J. M., Flodman, P., Kennedy, J., Spence, M. A., Moyzis, R., Schuck, S., et al. (2000). Dopamine genes and ADHD. *Neuroscience & Biobehavioral Reviews*, *24*, 21–25.

Tamm, L., Menon, V., & Reiss, A. L. (2006). Parietal attentional system aberrations during target detection in adolescents with attention deficit hyperactivity disorder, event-related fMRI evidence. *American Journal of Psychiatry*, *163*, 1033–1043.

Tamm, L., Menon, V., Ringel, J., & Reiss, A. L. (2004). Event-related FMRI evidence of frontotemporal involvement in aberrant response inhibition and task switching in attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *43*, 1430–1440.

Thapar, A., Holmes, J., Poulton, K., & Harrington, R. (1999). Genetic basis of attention deficit and hyperactivity. *British Journal of Psychiatry*, *174*, 105–111.

Vaidya, C. J., Austin, G., Kirkorian, G., Ridlehuber, H. W., Desmond, J. E., Glover, G. H., et al. (1998). Selective effects of methylphenidate in attention deficit hyperactivity disorder, a functional magnetic resonance study. *Proceedings of the National Academy of Sciences of the United States of America*, *95*, 14494–14499.

Vaidya, C. J., Bunge, S. A., Dudukovic, N. M., Zalecki, C. A., Elliott, G. R., & Gabrieli, J. D. (2005). Altered neural substrates of cognitive control in childhood ADHD, evidence from functional magnetic resonance imaging. *American Journal of Psychiatry*, *162*, 1605–1613.

Wilens, T. E., Biederman, J., & Spencer, T. J. (2002). Attention deficit/hyperactivity disorder across the lifespan. *Annual Review of Medicine*, *53*, 113–131.

Wilson, M. C. (2000). Coloboma mouse mutant as an animal model of hyperkinesis and attention deficit hyperactivity disorder. *Neuroscience Biobehavioral Reviews*, *24*, 51–7.

Zang, Y. F., Jin, Z., Weng, X. C., Zhang, L., Zeng, Y. W., Yang, L., et al. (2005). Functional MRI in attention-deficit hyperactivity disorder: Evidence for hypofrontality. *Brain & Development*, *27*, 544–550.

https://doi.org/10.1017/S0954579408000539 Published online by Cambridge University Press