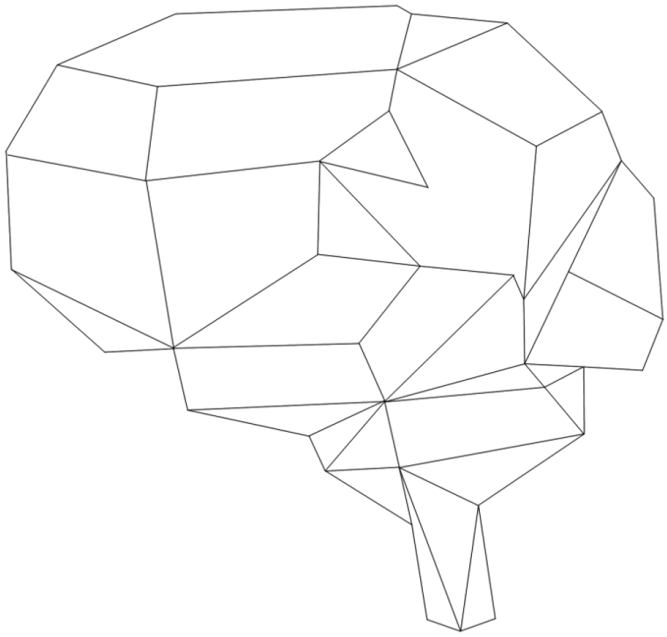
Stimulants and the developing brain

Schweren, Lizanne Johanna Stephanie

Chapter 2

MR IMAGING OF THE EFFECTS OF METHYLPHENIDATE ON BRAIN STRUCTURE AND FUNCTION IN ADHD



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ABSTRACT

Methylphenidate is the first-choice pharmacological intervention for the treatment of attention-deficit/hyperactivity disorder (ADHD). The pharmacological and behavioral effects of methylphenidate are well described, but less is known about neurochemical brain changes induced by methylphenidate. This level of analysis may be informative on how the behavioral effects of methylphenidate are established. This paper reviews structural and functional MRI studies that have investigated effects of methylphenidate in children with ADHD. Structural MRI studies provide evidence that long-term stimulant treatment may normalize structural brain changes found in the white matter, the anterior cingulate cortex, the thalamus, and the cerebellum in ADHD. Moreover, preliminary evidence suggests that methylphenidate treatment may normalize the trajectory of cortical development in ADHD. Functional MRI has provided evidence that methylphenidate administration has acute effects on brain functioning, and even suggests that methylphenidate may normalize brain activation patterns as well as functional connectivity in children with ADHD during cognitive control, attention, and during rest. The effects of methylphenidate on the developing brain appear highly specific and dependent on numerous factors, including biological factors such as genetic predispositions, subject-related factors such as age and symptom severity, and task-related factors such as task difficulty. Future studies on structural and functional brain changes in ADHD may benefit from inclusion strategies guided by current medication status and medication history. Further studies on the effects of methylphenidate treatment on structural and functional MRI parameters are needed to address unresolved issues of the long-term effects of treatment, as well as the mechanism through which medication-induced brain changes bring about clinical improvement.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is the most common developmental disorder in childhood, estimated to affect three to seven percent of school-age children and 2.5 percent of adults globally (Polanczyk et al., 2007; Simon et al., 2009). ADHD is characterized by age-inappropriate attention problems, and/or impulsivity and hyperactivity (American Psychiatric Association, 2000). The clinical presentation of ADHD is heterogeneous and comorbidity with oppositional defiant disorder (ODD), conduct disorder (CD), other neurodevelopmental disorders, mood and anxiety disorders is frequent (Pliszka, 2000). ADHD is regarded as an etiologically multifactorial disorder, with most likely both genetic and environmental factors influencing the clinical presentation (APA, 2000; Plomp et al., 2009).

Stimulant treatment remains the most common pharmacological intervention in ADHD and is effective for the majority of affected individuals (e.g., Barbaresi et al., 2006). Methylphenidate, available in various forms of delivery, is commonly regarded as the first-choice stimulant intervention (Meijer et al., 2009). Treatment is generally well tolerated and side-effects are typically mild (Greenhill et al., 2002; Wilens et al., 2006). Robust behavioral effects of stimulants have been reported, and include reduced symptoms of hyperactivity and inattention (Conners, 2002; MTA Cooperative Group, 1999; Spencer et al., 1996; Swanson et al., 1993).

The pharmacological properties of methylphenidate have been well investigated (Heal et al., 2009). Changes in the levels of dopamine and norepinephrine in the brain have frequently been associated with ADHD (Del Campo et al., 2011). A growing body of evidence suggests that methylphenidate increases the levels of dopamine and norepinephrine in the synaptic cleft, thereby stimulating their receptors (e.g., Arnsten, 2006; Kuczenski et al., 1997; Volkow et al., 2001). However, the question remains how these neurochemical methylphenidate-induced changes in the synapse result in the clinical and behavioral effects of methylphenidate treatment (Winstanley et al., 2006). Moreover, much remains unknown about the manifestation of such neurochemical effects in structural brain development, and its behavioral correlates. One approach to addressing these questions is to make use of modern neuroimaging techniques such as magnetic resonance imaging (MRI). Neuroimaging has the potential to provide researchers with relevant biomarkers, or clinically relevant characteristics that may be objectively measured as an indicator of pharmacological responses to therapeutic intervention (Minzenberg, 2012).

In recent years, structural and functional neuroimaging has been used to investigate the effects of medication on macroscopic brain measures in a variety of psychiatric disorders, including depression and schizophrenia (Honey & Bullmore, 2004). Not only have these studies contributed to our understanding of the brain

mechanisms which may drive the clinical effect of pharmacological treatments for these psychiatric disorders, but they have also advanced our understanding of the mechanisms underlying these disorders themselves (Doyle et al., 2005). Whereas direct pharmacological effects of methylphenidate have been investigated using the more invasive methods of positron emission tomography (PET) and SPECT, magnetic resonance imaging (MRI) is a tool more apt to studying macroscopic brain effects of methylphenidate. MRI has undergone rapid technological progression in recent years, allowing for the investigation of both structural and functional correlates of pharmacological treatment. In addition, MRI is a noninvasive tool, permitting its use in children, and is available in many research institutions (Honey & Bullmore, 2004).

Since the advent of MRI, several reports have appeared on the effects of methylphenidate on brain measures derived from MRI. Recent extensive and high-quality studies of methylphenidate effects (e.g., Rubia et al., 2009, 2011a and 2011b) have shown significant effects of methylphenidate. Owing to the high degree of specialization of such investigations, an increasingly detailed and complex picture emerges of the effects of methylphenidate on the developing brain. In an attempt to integrate such detailed descriptions of methylphenidate effects, this paper reviews the effects of childhood methylphenidate treatment on structural and functional MRI measures. Both acute and long-term effects of psychostimulant treatment will be addressed.

METHODS

This paper provides a systematic narrative review of the currently available MRI studies addressing the macroscopic effects of methylphenidate on the developing brain. The online databases of the US National Library of Medicine and the National Institutes of Health (PubMed), of the American Psychological Association (PsychInfo), and Web of Science were searched for relevant articles. In addition, reference lists of relevant articles were searched. Keywords for the search included ADHD, methylphenidate, MRI, fMRI, and neuroimaging. All abstracts that met these search criteria were read, and we selected those articles that (1) were written in English, (2) addressed the effects of methylphenidate administration during childhood (as opposed to drug administration during adulthood) in individuals with ADHD (as opposed to in other diagnostic groups), and (3) used magnetic resonance imaging (MRI) as a neuroimaging tool. When eligibility for inclusion in the review was doubted, the authors discussed and included the paper only upon consensus. Our search resulted in a total of 27 articles published between November 1998 and March 2012, including 26 original research articles and one meta-analysis/review article.

RESULTS

The effects of methylphenidate on brain structure in children with ADHD

A large and growing number of structural MRI studies document neuroanatomical changes between children with ADHD and typically developing controls (Durston et al., 2009; Seidman et al., 2005, Valera et al., 2007). A decrease in global brain volume has been reported in children and adolescents with ADHD compared to typically developing children, as well as local volume reductions in the frontal cortex, caudate nucleus, the cerebellum, and the corpus callosum, among other brain regions (Seidman et al., 2005; Valera et al., 2007). However, the long-term effects of stimulant treatment on these structural changes have received little attention. Studies that have specifically targeted such analyses are summarized in Table 1. Importantly, all studies investigating the effects of stimulant treatment on structural MRI measures are naturalistic in nature, and all except one (Shaw et al., 2009) employ a cross-sectional design (Table 1). Although this approach may be the most feasible approach to studying long-term treatment effects in children, the limitations of naturalistic, cross-sectional study designs need to be kept in mind when interpreting the results.

A small number of volumetric studies have compared volumes of specific brain regions (usually gray matter) between children with ADHD who were medication-naïve, children with ADHD who had been using medication, and typically developing children. An early study investigated total cerebral and cerebellar gray matter volume, as well as gray matter volume in the four major lobes, in these three groups. Compared to typically developing children, both medicated and medication-naïve subjects with ADHD showed reduced gray matter volumes, suggesting that gray matter volumes may not be affected by methylphenidate treatment (Castellanos et al., 2002). More recently, the majority of studies have turned to a hypothesis-driven region of interest (ROI) approach, where the volume of an a priori defined brain region was compared between groups. With this approach, medication effects have been found in the anterior cingulate cortex (ACC; Semrud-Clikeman et al., 2006), the pulvinar nucleus of the thalamus (Ivanov et al., 2010), and in the posterior inferior cerebellum (Bledsoe et al., 2009). Compared to typically developing children, children with ADHD who had not been treated with stimulants had significant volume reductions in these regions. These ADHD-related volume reductions did not occur, or were attenuated, in children who had been medicated with psychostimulants. No such effect of stimulant treatment was found in the caudate nucleus (Castellanos et al., 2002), although one study investigating a small sample of children with ADHD, the majority of them diagnosed with comorbid CD, suggested smaller caudate nucleus

volumes in previously medicated children with ADHD compared to medication-naïve children with ADHD (Bussing et al., 2002).

TABLE 1. Structural magnetic resonance imaging studies investigating the effects of methylphenidate treatment in children with ADHD.

Study	Main findings	
Castellanos et al. (2002)	Design:	TDC vs. $ADHD_{on}$ vs. $ADHD_{off}$. Volumetric study of the gray and white matter in frontal, temporal, parietal and occipital lobes, basal ganglia and cerebellum
	Subjects:	N_{TDC}=139, $N_{ADHD\text{-}off}$=103, $N_{ADHD\text{-}on}$=49; age range 5–19
	Findings:	Children with ADHD had smaller cerebral volumes, smaller cerebellar volumes, and smaller temporal gray matter volumes than TDC. MPH affected WM but not GM volumes. WM volumes in non-medicated children with ADHD were smaller than in TDC, while medicated children with ADHD did not show WM volume reductions
	Limitations:	4, 5
Bussing et al. (2002)	Design:	$ADHD_{off}$ vs. $ADHD_{on}$
	Subjects:	N_{TDC}=19, $N_{ADHD\text{-}off}$=7, $N_{ADHD\text{-}on}$=5; age range 8–12
	Findings:	Caudate nucleus volumes were smaller in medicated children with ADHD when compared to medication-naïve children with ADHD
	Limitations:	1, 2, 4, 5, 6
Semrud-Clikeman et al. (2006)	Design:	TDC vs. $ADHD_{off}$ vs. $ADHD_{on}$
	Subjects:	N_{TDC}=21, $N_{ADHD\text{-}off}$=14, $N_{ADHD\text{-}on}$=16; age range 9–15
	Findings:	Caudate nucleus and ACC volume were investigated. MPH did not affect caudate nucleus volume. Compared to in TDC, right ACC volume was decreased in medication-naïve children with ADHD, but not in medicated children with ADHD. A similar trend was found in the left ACC
	Limitations:	4, 5, 6
Bledsoe et al. (2009)	Design:	TDC vs. $ADHD_{off}$ vs. $ADHD_{on}$
	Subjects:	N_{TDC}=15, $N_{ADHD\text{-}off}$=14, $N_{ADHD\text{-}on}$=18; mean age=11.5(2.5)
	Findings:	Overall cerebellar volume was the same in all three groups. There were no volumetric group differences in the anterior or posterior superior vermis of the cerebellum. The inferior vermis of the cerebellum was smaller in non-medicated children with ADHD compared to both medicated children with ADHD and TDC
	Limitations:	4, 5, 6
Shaw et al. (2009)	Design:	$ADHD_{off}$ vs. $ADHD_{on}$ vs. template of cortical development based on TDC participants
	Subjects:	N_{TDC}=294, $N_{ADHD\text{-}off}$=19, $N_{ADHD\text{-}on}$=24, age range 9–20
	Findings:	At baseline, no group differences in cortical thickness were

		found between the three groups, but both ADHD groups contained children with a history of stimulant medication. At follow-up, cortical thickness did not differ between controls and medicated children with ADHD, while non-medicated children with ADHD showed a higher rate of cortical thinning in the IFG, the right precentral gyrus, and right parieto-occipital gyrus
	Limitations:	3, 5, 7
Ivanov et al. (2010)	Design:	TDC vs. $ADHD_{off}$ vs. $ADHD_{on}$
	Subjects:	N_{TDC}=59, $N_{ADHD\text{-}off}$=15, $N_{ADHD\text{-}on}$=31, age range 8–18
	Findings:	Children with ADHD had reduced regional volumes of thalamic surfaces, including the pulvinar nucleus. Medicated children with ADHD had larger pulvinar volumes than their non-medicated peers
	Limitations:	4, 5, 6, 7
De Zeeuw et al. (2012)	Design:	TDC vs. ADHD, and $ADHD_{long\text{-}medication}$ vs. $ADHD_{short\text{-}medication}$
	Subjects:	N_{TDC}=34, N_{ADHD}=30, $N_{ADHD\text{-}long\text{-}medication}$=13, $N_{ADHD\text{-}short\text{-}medication}$=13, age range 6–16
	Findings:	Microstructural abnormalities were observed in frontostriatal WM in children with ADHD. Medication duration (long vs. short) was calculated relative to the children's age. Exploratory analyses showed no effect of treatment duration on these abnormalities
	Limitations:	4, 5, 6
Nakao et al. (2011)	Design:	TDC vs. ADHD, meta-regression of 9 pediatric VBM datasets
	Subjects:	N_{TDC}=198, N_{ADHD}=202
	Findings:	In a VBM meta-analysis of regional GM volumes, children with ADHD showed GM volume decrease in the right caudate nucleus, and GM volume increase in the left precuneus cortex. In studies including a larger percentage of medicated children with ADHD, right caudate nucleus volume was larger, thus more normal, compared to in studies including a smaller percentage of medicated children with ADHD. No medication effect was found in the precuneus cortex
	Limitations:	4, 5, 7

$ADHD_{on}$, children with ADHD receiving stimulant treatment; $ADHD_{off}$, children with ADHD not receiving stimulant treatment; TDC, typically developing controls; MPH, methylphenidate; CD, conduct disorder; GM, gray matter; WM, white matter; ACC, anterior cingulate cortex; IFG, inferior frontal gyrus; VBM, voxel-based morphometry. Study limitations are coded as follows: 1=small sample size (N<45 or n per group/condition <15); 2=no direct between-group comparison between TDC, $ADHD_{medicated}$ and $ADHD_{non\text{-}medicated}$ is reported; 3=medication history prior to study participation is unknown/not reported; 4=cross-sectional study design: no within-subject analysis of medication effects; 5=naturalistic study design: no randomized clinical trial; 6=selective analyses of brain regions; 7=medication group/condition includes pharmacological treatment other than MPH

Another approach to investigating structural changes in the brain involves data-driven methods, where large brain areas are investigated without an a-priori hypothesis, such as with voxel-based morphometry (VBM) or cortical thickness measurements. In VBM, individual scans are normalized to a template brain, effectively comparing gray and white matter volume between groups in each voxel of the brain, rather than in specific anatomical brain regions of interest (Ashburner & Friston, 2000). In a meta-analysis of VBM studies in ADHD, a medication effect was found in the right basal ganglia (Nakao et al., 2011). Across individuals with ADHD, gray matter volume in the right caudate nucleus was decreased. However, the percentage of medicated subjects in the studies included in this meta-analysis correlated positively with gray matter volume in the right caudate nucleus. In studies with a larger percentage of medicated children, right caudate nucleus volume was larger, thus more normal, compared to in studies including a smaller percentage of medicated children. No such medication effect was found in the left precuneus that showed increased volume in children with ADHD compared to controls (Nakao et al., 2011). Cortical thickness analyses provide a more direct measure of the thickness of the outer gray matter layer of the cerebrum than volumetric analyses can provide. Shaw et al. (2009) applied such analyses in a unique longitudinal study, and found that unmedicated children with ADHD showed excessive cortical thinning compared to typically developing children during adolescence, whereas children with ADHD receiving stimulant medication during the period of study did not. This study suggests that stimulant treatment may reduce the rate of cortical thinning in frontal and parieto-occipital regions during adolescence.

Methylphenidate treatment may also affect measures of white matter structure (Table 1). For example, cerebral white matter volume was found to be reduced in medication-naïve children with ADHD compared to typically developing children, but also compared to previously medicated children with ADHD. In fact, children with ADHD with a history of psychostimulant use showed no changes in total white matter volume, or in white matter volume in any of the four major lobes, suggesting that methylphenidate treatment may normalize white matter volume reductions in children with ADHD (Castellanos et al., 2002). In line with this, two studies investigating white matter volume that included previously medicated subjects with ADHD only, reported no evidence for white matter volume reduction (Batty et al., 2010; Carmona et al., 2005). Unfortunately, in a meta-analysis of volumetric studies, Valera et al. (2007) were unable to assess possible effects of stimulant medication on white matter volume, due to a lack of information regarding medication status and history. A recent study that investigated the microstructure of frontal-striatal white matter tracts in children with ADHD using diffusion tensor imaging (DTI) found decreased structural connectivity within these tracts (De Zeeuw

et al., 2012). An exploratory analysis of the effects of stimulant medication compared subjects that had been medicated for a relatively long period with subjects that had been medicated for a shorter period. No significant effect of treatment duration on microstructural abnormalities was found (De Zeeuw et al., 2012). Thus, white matter volume may be affected by the use of stimulant medication, but the exact nature of these changes requires further investigation.

In conclusion, structural MRI studies have provided evidence that stimulant treatment may normalize specific, but not all, structural brain abnormalities found in children with ADHD, in both gray and white matter.

The effects of methylphenidate on patterns of brain activation in children with ADHD

In contrast to the few structural MRI studies investigating the effects of methylphenidate, there have been numerous functional MRI (fMRI) studies on the acute effects of methylphenidate (Table 2). Such studies can be divided into those investigating spontaneous brain activation while at rest (resting-state fMRI), and those investigating task-related brain activation. Two resting-state fMRI studies, employing T2 relaxometry as an indirect measure of cerebral blood volume, suggested that methylphenidate may have an acute normalizing effect on striatal (Teicher et al., 2000) and cerebellar (Anderson et al., 2002) activation in boys with ADHD during rest. Task-related fMRI studies on the effects of methylphenidate have been more numerous and have often focused on cognitive domains implicated in ADHD, and where performance is known to improve with methylphenidate administration. A fairly consistent overall picture of the acute effects of methylphenidate administration emerges across various experimental designs.

During tasks tapping cognitive control, the ability to inhibit inappropriate responses in favor of more appropriate ones, methylphenidate appeared to normalize brain activation patterns in children with ADHD by enhancing activation in frontostriatal circuits (Epstein et al., 2007; Lee et al., 2010; Rubia et al., 2011b; Vaidya et al., 1998). A similar upregulation of activation towards activation levels of typically developing children was found in parietal brain regions (Rubia et al., 2011a). Furthermore, methylphenidate administration was found to overcome deficits in the suppression of default mode network (DMN) activity, or activity within a network of brain regions typically deactivated during goal-directed behavior: during cognitive control tasks, children with ADHD were shown to fail to suppress activation within this network, and methylphenidate was found to restore DMN suppression towards the levels of typically developing children (Peterson et al., 2009).

The effects of methylphenidate on behavioral measures of attention problems are well established (e.g., MTA Cooperative Group, 1999). Cognitive tasks measuring

aspects of attention, such as the ability to sustain attention over time, or to divide attentional resources amongst subtasks, are frequently used in fMRI studies of ADHD. Methylphenidate appeared to at least partially normalize brain activation patterns in children with ADHD during divided attention (Rubia et al., 2009; Shafritz et al., 2004). In addition, methylphenidate has been shown to restore functional connectivity, or synchronized activity, in disparate but functionally related brain regions, in networks involved in attention in children with ADHD (Rubia et al., 2009). Interestingly, methylphenidate administration may also elicit non-normalizing, additional activity in the brain. During vigilance, a basic form of sustained attention, methylphenidate administration was found to elicit compensatory activation in the prefrontal cortex of children with ADHD that was not evident in typically developing children (Rubia et al., 2009).

By contrast, studies investigating the effects of methylphenidate on activation patterns during working memory tasks have yielded inconsistent results. During working memory, stimulant administration elicited increases of activation in the frontal cortex (Prehn-Kristensen et al., 2011) and in frontal-parietal networks (Wong & Stevens, 2012), but not in the striatum (Prehn-Kristensen et al., 2011). However, opposing findings of reduction of prefrontal cortex activity by methylphenidate administration (Sheridan et al., 2010) or no effect of medication on frontal-striatal activation (Kobel et al., 2009) have also been reported. The lack of a control group in some of these studies (Sheridan et al., 2010; Wong & Stevens, 2012) and the absence of a placebo condition in others (Kobel et al., 2009; Prehn-Kristensen et al., 2011), may contribute to the conflicting findings, and limits the interpretation of the results. Studies investigating stimulant effects on regional functional connectivity during working memory tasks have similarly yielded inconsistent results. In a pilot study in adolescent girls with ADHD, stimulant medication decreased functional connectivity during a working memory task (Sheridan et al., 2010). By contrast, Wong and Stevens (2012) found that stimulant medication increased functional connectivity between frontostriatal brain structures and other brain regions in children with ADHD during a working memory task. However, since both studies did not include a control group, it is unclear how these methylphenidate-induced changes compare to functional brain connectivity during working memory in typically developing children.

In contrast to the numerous studies investigating the acute effects of methylphenidate administration, only two studies have investigated the effects of long-term methylphenidate treatment on brain activation patterns in children with ADHD. Overall, after wash-out, methylphenidate treatment appeared not to translate into long-lasting alterations of brain activation patterns, nor into normalization of functional brain development. During tasks tapping aspects of cognitive control (Konrad et al., 2007; Pliszka et al., 2006), no changes were found in overall brain

TABLE 2 Functional magnetic resonance imaging studies investigating the effects of methylphenidate administration in childhood ADHD

Domain	Study	Main findings	
Resting state	Teicher et al., 2000	Subjects:	N_{TDC}=6; N_{ADHD}=11; Age range 6–12
		ADHD *vs.* TDC:	Children with ADHD showed lower bilateral putamen activation, but normal thalamic and caudate activation
		MPH effects:	MPH increased putamen activation in hyperactive children with ADHD, but decreased putamen activation in non-hyperactive children with ADHD. MPH did not affect thalamic or caudate activation
		Limitations:	1,4,5,7
	Anderson et al., 2002	Subjects:	N_{TDC}=6; N_{ADHD}=10; Mean age 9.6(1.6)
		ADHD *vs.* TDC:	No analyses
		MPH effects:	MPH decreased activity of the cerebellar vermis, but not the cerebellar hemispheres, in hyperactive children with ADHD. MPH increased activity of the cerebellar vermis in non-hyperactive children with ADHD
		Limitations:	1.3.4.5.7
Response inhibition	Vaidya et al., 1998	Subjects:	N_{TDC}=6; N_{ADHD}=10; Age range 8–13
		ADHD *vs.* TDC:	Children with ADHD showed decreased striatal activation, and increased frontal activation
		MPH effects:	MPH increased striatal activation in children with ADHD, but decreased striatal activation in typically developing subjects. MPH increased frontal activation in both children with ADHD and typically developing children
		Limitations:	1,4,7
	Zang et al., 2005	Subjects:	N_{TDC}=9; N_{ADHD}=9; Age range 9–15
		ADHD *vs.* TDC:	Typically developing children showed a 'neuronal Stroop effect' in brain activation patterns, in which brain activation during non-congruent Stroop-trials was larger than during congruent Stroop-trials. Children with ADHD showed the opposite pattern, congruent trials eliciting more brain activation than non-congruent trials
		MPH effects:	MPH tended to restore the neuronal Stroop effect in children with ADHD towards the pattern seen in typically developing children

TABLE 2 *Continued*

Domain	Study	Main findings	
		Limitations:	1,3,7,9
	Pliszka et al., 2006	Subjects:	N_{TDC}=15; N_{ADHD}=17; Age range 9–15
		ADHD *vs.* TDC:	Overall, comparable activation was found in the ACC, dorsolateral PFC, and ventrolateral PFC, in typically developing children, medication-naïve children with ADHD, and previously medicated children with ADHD. During incorrect responses, typically developing children showed increased ACC activation compared to during correct responses, while medication-naïve children with ADHD showed the opposite pattern
		MPH effects:	One year MPH treatment increased ACC activation during incorrect responses, but not to TDC levels
		Limitations:	1,5,6,7
	Epstein et al., 2007	Subjects:	N_{TDC}=9; N_{ADHD}=20; Age range 7–9
		ADHD *vs.* TDC:	Children with ADHD showed decreased activation in the frontal lobe, the ACC, the inferior parietal cortex, and caudate nucleus
		MPH effects:	MPH increased activation in the frontal lobe, the ACC, the inferior parietal cortex, the caudate nucleus and the cerebellum
		Limitations:	1,3,7
	Peterson et al., 2009	Subjects:	N_{TDC}=20; N_{ADHD}=16; Age range 7–18
		ADHD *vs.* TDC:	During a Stroop task, children with ADHD showed less prominent task-related deactivation of the DMN than typically developing subjects. Functional connectivity between the Lateral PFC and the ACC was reduced in children with ADHD
		MPH effects:	MPH restored task-related deactivations in the DMN, and increased functional connectivity between the LPFC and the ACC
		Limitations:	4
	Lee et al., 2010	Subjects:	N_{ADHD}=8; Age range 9–11
		MPH effects:	During interference suppression, MPH increased activation in the right PFC. There were no effects of MPH during response inhibition
		Limitations:	1,2,3,4,9

TABLE 2 *Continued*

Domain	Study	Main findings	
	Rubia et al., 2011a	Subjects:	N_{TDC}=13; N_{ADHD}=13; Age range 10–16
		ADHD *vs.* TDC	During interference inhibition, boys with ADHD showed reduced activity in the right inferior PFC, left striatum and thalamus, mid-cingulate/SMA region, and left superior temporal lobe
		MPH effects:	MPH administration resulted in an upregulation of activity in the right inferior prefrontal cortex and in premotor areas in children with ADHD. While on MPH, children with ADHD
		Limitations:	1
Working Memory	Kobel et al., 2009	Subjects:	N_{TDC}=12; N_{ADHD}=14; Age range 9–13
		ADHD *vs.* TDC:	Children with ADHD showed less activation in the frontal and parietal regions, and failed to recruit the cerebellum. Left sided frontal and parietal activation was more reduced
		MPH effects:	No effects of MPH were found
		Limitations:	1,4,10
	Sheridan et al., 2010	Subjects:	N_{ADHD}=5; Age range 11–17
		MPH effects:	MPH decreased PFC activation and functional connectivity between frontal and subcortical regions. MPH increased connectivity between the MFG and the cerebellar vermis
		Limitations:	1,2,3,4,7,8,10
	Prehn-Kristensen et al., 2011	Subjects:	N_{TDC}=12; N_{ADHD}=12; Age range 10–17
		ADHD *vs.* TDC:	In the non-distracted task, children with ADHD showed reduced frontal activation compared to typically developing children. In the distracted task, children with ADHD showed a lack of caudate nucleus activation
		MPH effects:	MPH restored frontal activation during the non-distracted task to normal levels. MPH did not restore caudate nucleus activation during the distracted task
		Limitations:	1,4,10
	Wong & Stevens, 2012	Subjects:	N_{ADHD}=18; Age range 11–17
		MPH effects:	Stimulant medication increased the magnitude of frontoparietal network activation during a working memory task. Moreover, stimulant medication increased regional functional connectivity between frontoparietal network structures and other brain regions

TABLE 2 *Continued*

Domain	Study	Main findings	
		Limitations:	2,3,4
Attention	Shafritz et al., 2004	Subjects:	N_{TDC}=14; N_{ADHD}=27; Age range 12–20
		ADHD *vs.* TDC:	During tasks of selective and divided attention, children with ADHD showed less activation in the left basal ganglia and the middle temporal gyrus
		MPH effects:	MPH increased activation in the left basal ganglia, but not in the middle temporal gyrus
		Limitations:	-
	Konrad et al., 2007	Subjects:	N_{TDC}=14; N_{ADHD}=16; Mean age 11.3(1.3)
		ADHD *vs.* TDC:	Whereas typically developing children showed increase in ACC and TPJ activation during attention processes over the course of one year, children with ADHD (regardless of medication status) did not
		MPH effects:	MPH did not elicit developmentally appropriate increases in ACC and TPJ activation. However, whereas non-medicated children showed developmentally inappropriate activation of the insula and striatum during reorienting of attention, this possibly compensatory activation was not present in children that received one year of stimulant treatment
		Limitations:	1,3,6
	Rubia et al., 2009	Subjects:	N_{TDC}=13; N_{ADHD}=13; Age range 10–16
		ADHD *vs.* TDC:	During selective attention, children with ADHD showed reduced activation and functional connectivity in fronto-striato-parieto-cerebellar networks
		MPH effects:	MPH increased fronto-striato-cerebellar and parieto-temporal activation, as well as fronto-striatal and fronto-cerebellar connectivity
		Limitations:	1
Reward processing	Rubia et al., 2009	Subjects:	N_{TDC}=13; N_{ADHD}=13; Age range 10–16
		ADHD *vs.* TDC:	During reward processing, children with ADHD showed increased orbito-frontal and superior temporal activation
		MPH effects:	MPH decreased orbito-frontal activation
		Limitations:	1

TABLE 2 *Continued*

Domain	Study	Main findings	
	Stoy et al., 2011	Subjects:	N_{TDC}=12; $N_{ADHD\text{-}untreated}$=12; $N_{ADHD\text{-}treated}$=11; Mean age 27.5(4.6)
		ADHD *vs.* TDC:	Activation in the ventral striatum and OFC were equal in TDC adults, adults with ADHD who had been treated during childhood, and adults with ADHD who had not
		MPH effects:	During loss avoidance, insula activation was lower in drug-naïve subjects in comparison to both TDC and previously treated groups
		Limitations:	1,5,6,7
Error processing	Rubia et al., 2011b	Subjects:	N_{TDC}=13; N_{ADHD}=12; Age range 10–16
		ADHD *vs.* TDC:	During failed response inhibition, or error monitoring, boys with ADHD showed reduced brain activation in the dorsomedial and left ventrolateral PFC, the thalamus, cingulate, and parietal areas. During successful response inhibition, boys with ADHD showed underactivation in the right medial temporal and inferior parietal lobe, the precuneus and the cerebellum
		MPH effects:	During both failed and successful inhibition, MPH restored activation patterns to the levels of typically developing children. No differences between brain activation patterns of children with ADHD on MPH and typically developing children were observed
		Limitations:	1
Emotion processing	Schlochtermeier et al., 2011	Subjects:	N_{TDC}=10; $N_{ADHD\text{-}untreated}$=10; $N_{ADHD\text{-}treated}$=10; Mean age 28.4(5.2)
		ADHD *vs.* TDC:	No analyses
		MPH effects:	MPH-naïve adults with childhood ADHD, but not adults with ADHD who had been treated with MPH during childhood, showed decreased activation in the subgenual cingulate and the ventral striatum compared to TDC
		Limitations:	1,5,6,7

$ADHD_{on}$, subjects with ADHD receiving stimulant treatment; $ADHD_{off}$, subjects with ADHD not receiving stimulant treatment; TDC, typically developing control subjects; MPH, methylphenidate; ACC, anterior cingulate cortex; VBM, voxel-based morphometry; TPJ, temporo-parietal junction; PFC, prefrontal cortex; DMN, default mode network; RI, response inhibition; MFG, medial frontal gyrus. Study limitations are coded as follows: 1=small sample size (n per group/condition<15); 2=absence of control group/condition; 3=no direct between-group comparison between TDC, $ADHD_{on\text{-}medication}$ and $ADHD_{off\text{-}medication}$ is reported; 4=medication history prior to study participation is unknown/not reported; 5=cross-sectional study design: no within-subject analysis of medication effects; 6=naturalistic study design: no randomized clinical trial; 7=selective analyses of brain regions; 8=medication group/condition includes pharmacological treatment other than MPH; 9=statistical testing is not reported for all contrasts of interest; 10=absence of placebo group/condition

activation patterns between children who had previously received long-term methylphenidate treatment, and children who had not. Observed long-term methylphenidate treatment effects were restricted to highly specific tasks and brain regions. By contrast, two recent fMRI studies in currently non-medicated adults with ADHD that specifically investigated the effect of stimulant treatment history during childhood did find evidence of lasting medication effects on brain activation patterns. Methylphenidate-naïve adult subjects with ADHD showed changes in brain activation during emotional processing (Schlochtermeier et al., 2011) and during reward processing (Stoy et al., 2011) compared to typical control subjects, whereas adult subjects with ADHD who had received methylphenidate treatment during childhood did not. This suggests that childhood methylphenidate treatment may result in normalization of brain activation patterns in adulthood, similar to the acute functional normalization after methylphenidate administration in children with ADHD. However, opposing findings of larger functional brain abnormalities in adult ADHD subjects with a history of stimulant treatment, compared to subjects without a history of stimulant treatment, have also been reported (Ludolph et al., 2008).

Importantly, these studies have limitations (Table 2). First, for many cognitive domains, the effects of methylphenidate have only been investigated once or twice. As such, replication is clearly needed. Second, sample sizes are typically small, with the majority of studies investigating fewer than fifteen subjects per group or condition. Third, only a small minority of these studies are randomized, double-blind, placebo-controlled trials (Rubia et al., 2011a and 2011b; Wong & Stevens 2012), limiting the inferences that can be drawn from the literature currently available. Fourth, studies tend to range widely in terms of inclusion criteria and the selection of cognitive tasks, further complicating direct comparison of their results and this may well contribute to the discrepant outcomes between studies. For instance, a subject's medication history (medication-naïve *vs.* previously medicated, as well as medication duration and dosage in the past) may influence the effects of acute methylphenidate administration on the brain, but remains undisclosed in several of the fMRI studies (e.g., Peterson et al., 2009; Teicher et al., 2000; Vaidya et al., 1998). Finally, although all studies investigating acute effects of methylphenidate administration ensured a wash-out period prior to study participation, acute rebound effects after sudden cessation of medication cannot be controlled for.

DISCUSSION

Methylphenidate effects are likely to be highly specific and rate-dependent

Based on the literature to date, methylphenidate administration appears to elicit functional and structural changes throughout the brain. The results of the studies reported in Table 1 and Table 2 suggest that the direction of methylphenidate effects may be related to the specific neural changes in ADHD. Different cognitive paradigms elicit different brain activation patterns, and therefore are associated with differing changes in brain activity with methylphenidate administration. Functional neuroimaging studies have suggested that methylphenidate induces acute normalization of activation patterns in widespread regions of the brain, including brain regions that have been associated with structural and functional changes in ADHD. However, the direction of these methylphenidate-induced functional changes varied. For example, reduced ACC activity was found in children with ADHD during a cognitive control task, which increased with methylphenidate administration (Epstein et al., 2007), while another study found that methylphenidate enhanced task-related deactivation in the ACC in children with ADHD (Peterson et al., 2009). A third study, by contrast, has found that typically developing children, but not children with ADHD, showed increased ACC activity during incongruent Stroop-trials compared to during neutral trials, and that this lack of increase in ACC activity in ADHD was restored by methylphenidate administration (Zang et al., 2005). Thus, whereas all three studies report acute normalization of ACC activation after methylphenidate administration, the effects of methylphenidate on the ACC differed between studies. The consistency of the normalization of brain activity patterns by methylphenidate suggests that its seemingly discrepant acute effects on brain activation patterns across studies do not merely represent conflicting findings. Rather, the effects of methylphenidate may be highly specific, depending on the presence or absence of ADHD-related functional changes in specific brain regions during the performance of specific cognitive tasks. Since unmedicated children with ADHD show regionally specific and task-dependent deficits in brain activation, the modulating effects of methylphenidate treatment on these functional changes may also be specific. In sum, the studies to date suggest that methylphenidate modulates activity levels towards the levels of typically developing children, regardless of whether the ADHD-related changes (i.e., without medication) constituted decreased or increased activity compared to typically developing controls.

The rate-dependency hypothesis suggests that the effects of methylphenidate treatment on brain activation may be dependent on the amount of 'baseline' activation (or activation while not on stimulant medication) in a particular brain region (Andersen, 2005). Thereby, methylphenidate may have a different effect on the

brain of subjects with ADHD than in typical controls. This issue is subject to intense debate, and is hard to address as ethical constraints disallow the administration of drugs to typically developing children. In the only study to address methylphenidate effects in both children with ADHD and typically developing children, Vaidya et al. (1998) used a cognitive control paradigm. Children with ADHD showed decreased striatal activation compared to typically developing children without methylphenidate, but showed an increase in striatal activation after methylphenidate administration. By contrast, typically developing children showed decreased activation of the striatum after methylphenidate administration (Vaidya et al., 1998). In typical adults, methylphenidate administration has been found to change brain activation patterns during a variety of cognitive functions, including working memory, attention and reversal learning (e.g., Dodds et al., 2008; Tomasi et al., 2011), but such changes have not been compared directly to methylphenidate-induced brain changes in adult subjects with ADHD.

Methylphenidate effects may be influenced by various biological, subject-related and task-related factors

Adding to the complexity of the rate-dependency hypothesis are numerous other factors, including biological, subject-related demographic, and task-related ones. All may affect baseline brain activation. By affecting brain activation patterns, these factors may also influence the effect of methylphenidate administration on these patterns. First, several biological factors may be at play. For example, neural activity levels while not on medication may be modulated by the density of neuronal dopamine receptors, which, in turn, seems to be genetically determined, at least partially (e.g., Bédard et al., 2010; Durston et al., 2008; Heinz et al., 2000). In typical adults, regional D2 receptor availability was found to be correlated to metabolic changes in the cerebellum, frontal and temporal regions induced by methylphenidate administration (Volkow et al., 1997). Thus, biological factors including genetic predispositions may determine, at least to some extent, how the brain responds to methylphenidate administration, via modulation of dopamine neurotransmission characteristics in an unmedicated state.

In addition to biological factors, subject-related demographic factors such as age and gender may contribute to regional brain activation patterns. Such factors could in turn influence the neural effects of methylphenidate treatment in a highly specific manner. Animal studies suggest that age at initiation of stimulant treatment is of particular importance (e.g., Canese et al., 2009). The brain undergoes drastic changes in structural and functional organization during development. Although the mechanism of stimulant action is likely to be similar in the immature and mature

brain, the substrate that stimulants act on, i.e., the catecholaminergic system, develops with age (Andersen, 2005). This may result in different patterns of brain response to methylphenidate administration at different ages. For example, methylphenidate was found to increase frontostriatal and cerebellar activation in children with ADHD, whereas it increased striatal activation but decreased prefrontal and right parietal activation in adults with ADHD (Epstein et al., 2007). The effects of methylphenidate administration may differ not only between children and adults, but also over childhood. Moreover, each brain region has a unique developmental trajectory, which leads to a complex picture of brain regions each being more or less sensitive to stimulant treatment at different time points in development (Rapoport & Gogtay, 2008).

Finally, task-related factors may influence the effect of methylphenidate on the brain through the brain activation patterns they evoke. For example, a working memory task elicits different patterns of brain activation than a cognitive control task, and will therefore show functional changes in ADHD that are specific to that cognitive task or domain. As a result, possible methylphenidate-induced functional changes during a working memory task will differ from methylphenidate-induced changes during a cognitive control task. The same principle may apply to task difficulty. It has been suggested that functional brain changes in children with ADHD are more pronounced during cognitively demanding tasks than during less demanding tasks (e.g., Kobel et al., 2009; Vaidya et al., 1998; Zang et al., 2005). Consequently, the rate-dependency hypothesis implies larger methylphenidate effects during more difficult cognitive challenges. Indeed, normalization of brain activation patterns with methylphenidate appears more pronounced in cognitively more demanding tasks than in less demanding tasks (Shafritz et al., 2004; Vaidya et al., 1998). Interestingly, a recent study suggests that the effects of methylphenidate across cognitive tasks of increasing difficulty are finite (Prehn-Kristensen et al., 2011). In a relatively non-demanding working memory task, children with ADHD showed a lack of predominantly frontal activation compared to typically developing children, which was resolved by the administration of methylphenidate. When task difficulty was increased by adding distractors, typically developing children, but not children with ADHD, recruited the caudate nucleus. Whereas increasing task difficulty resulted in the additional recruitment of the caudate nucleus in typically developing children, this strategy was not brought about by methylphenidate administration in children with ADHD (Prehn-Kristensen et al., 2011). Thus, task characteristics, including task difficulty, may affect the detection of methylphenidate effects on the brain.

In sum, methylphenidate-induced changes in brain activation patterns may be dependent on the level of 'baseline' activation in the brain, which in turn is determined by a multitude of factors. As such, biological factors, subject-related

factors and task-related factors, amongst many, may influence methylphenidate-induced changes in the brain of children with ADHD. Thus, the available evidence suggests that methylphenidate treatment does not necessarily affect brain activity in the same way for all children with ADHD, similar to the way methylphenidate treatment also affects behavior differentially between children with ADHD (e.g., MTA Cooperative Group, 1999).

Behavioral correlates of methylphenidate-induced neural changes

This paper aimed to decrease the gap between the well-described physiological effects of methylphenidate in the synapse, and the beneficial effects of methylphenidate on ADHD symptoms. A growing body of work shows that methylphenidate affects MRI-based brain measures in children with ADHD, by normalizing both structural and functional changes observed in unmedicated subjects with ADHD. However, to investigate the mechanisms by which methylphenidate changes behavior it is important to relate these brain changes to behavioral outcome measures, such as ADHD symptom severity or task performance during functional MRI experiments.

The important issue of whether methylphenidate-induced brain changes in children with ADHD are accompanied by behavioral changes has rarely been addressed directly, and results have been inconsistent. Ivanov et al. (2010) found an association between behavioral ratings of hyperactivity and thalamus volume reduction in ADHD. Both ADHD symptoms and volume reductions were less severe in children who had been treated with psychostimulants. By contrast, Shaw et al. (2009) found that the excessive cortical thinning that occurred in children with ADHD that stopped taking psychostimulant medication, but not in children with ADHD that continued taking psychostimulant medication, was not associated with differences in clinical outcome between these two groups. Several methodological differences between studies, such as age of the studied sample, make these results hard to interpret. In their meta-analysis, Nakao et al. (2011) were unable to assess whether methylphenidate-induced structural changes were related to behavioral changes in children with ADHD, due to methodological discrepancies between studies. Diverse results also emerge from functional MRI studies. Whereas in some studies functional normalization was accompanied by symptom reduction or improved task performance (e.g., Anderson et al., 2002; Lee et al., 2010; Peterson et al., 2009; Prehn-Kristensen et al., 2011; Rubia et al., 2009; Teicher et al., 2000; Vaidya et al., 1998), others did not find such a relation (e.g., Epstein et al., 2007; Kobel et al., 2009; Rubia et al., 2011a; Shafritz et al., 2004).

Alternatively, one could regard behavioral measures while not on medication, such as symptom severity, as a subject-related factor associated with 'baseline' brain activity. Subjects with ADHD who are more severely behaviorally affected could present with more functional changes in the brain (Depue et al., 2010), which could hypothetically result in more pronounced changes in brain activation patterns after methylphenidate administration. As such, behavioral or clinical measures may be a possible predictor of methylphenidate-induced changes in brain activation patterns. Indeed, differential effects of methylphenidate administration on resting-state brain activity have been found for behaviorally hyperactive vs. non-hyperactive children with ADHD. More hyperactive children with ADHD showed larger effects of methylphenidate administration on resting-state activity in the striatum and cerebellum than less hyperactive children with ADHD (Anderson et al., 2002; Teicher et al., 2000). Clearly, more evidence is needed in order to understand the association between the structural and functional brain changes after methylphenidate administration on the one hand, and the clinical effects of psychostimulant treatment on the other.

Implications for neurobiological research into ADHD

A large proportion of children with ADHD receive stimulant treatment at some point in their life. As a result, researchers investigating the neural correlates of ADHD face a major methodological challenge: whereas including children with a history of stimulant treatment introduces a potential biasing effect of methylphenidate treatment into the study sample, excluding children with a history of stimulant treatment would greatly reduce the number of potential study participants, and would reduce generalizability of study results to the population of all individuals affected with ADHD. In practice, neuroimaging studies include subjects with or without a history of stimulant treatment, or a mixture of these groups.

The effects of methylphenidate on structural and functional MRI highlight the importance of monitoring medication status and medication history of study participants. Including medicated subjects with ADHD in structural MRI studies may result in reduced power to find structural brain changes that are relevant to the phenotype, given that treatment with methylphenidate appears to normalize brain development to some extent. Therefore, studies investigating neuroanatomical changes between subjects with ADHD and typically developing subjects may benefit from the inclusion of medication-naïve children with ADHD only. Alternatively, addressing the possible confounding effects of treatment history in a sample including participants with variable medication histories (e.g., De Zeeuw et al., 2012), may further our understanding of long-term methylphenidate effects. The acute

normalizing effects of methylphenidate on fMRI measures imply that functional deficits underlying ADHD symptoms may be less pronounced in an ADHD sample including medicated individuals, emphasizing the importance of medication wash-out prior to functional MRI scanning. Until today, no conclusive evidence of lasting functional alterations after methylphenidate treatment has been reported in children with ADHD. The long-term effects of stimulant treatment on functional MRI measures thus need further investigation.

Several hypotheses have been proposed on mechanisms underlying the brain effects of long-term methylphenidate treatment. It has been suggested that the effects of methylphenidate treatment on structural MRI measures could be an example of activity-induced neuronal plasticity (Ivanov et al., 2010; Semrud-Clikeman et al., 2006; Shaw et al., 2009). Stimulants are thought to increase catecholaminergic neurotransmission, which may influence cellular morphology (Robinson & Kolb, 2004). In addition, the increased catecholaminergic neurotransmission may lower the threshold for learning, or plasticity, allowing the brain to form new connections during cognitive tasks, resulting in volumetric changes. However, such hypotheses regarding possible biological mechanisms for long-term structural changes remain speculative. More direct measures of catecholaminergic neurotransmission, such as SPECT and PET, may be more informative than MRI in this regard (e.g., Fusar-Poli et al., 2012).

Limitations and future perspectives

This paper reviews the currently available studies on the effects of stimulant treatment on brain structure and functioning as assessed using MRI-based techniques, in children with ADHD. Although a meta-analytic review has benefits over a narrative review such as this one, the methods applied in the different studies vary strongly at this time. As such, the descriptive nature of this review reflects the current state of the literature. Any conclusions regarding the specificity of the effects of stimulant treatment on the developing brain therefore remain speculative, and are limited by the caveats inherent to the original research articles presented in Table 1 and Table 2.

Each of the reported studies has their own methodological drawbacks, but some of these are common across the literature. We mention five main issues. First, the majority of structural MRI studies have (of necessity) adopted a naturalistic, cross-sectional design. This does not allow for any conclusions on cause and effect or a more informative within-subject evaluation of stimulant treatment effects. Second, a major concern that applies to all but two functional MRI studies is small sample size, with sometimes less than fifteen subjects per group or condition. Third, several functional MRI studies have not provided information on the type or duration of

stimulant treatment. Fourth, a less common limitation, which is more common to structural MRI studies, has been the inclusion of children (albeit a small percentage of participants) who were being treated with non-stimulant medication, such as atomoxetine (e.g., Ivanov et al., 2010; Shaw et al., 2009). Fifth, both structural and, to a lesser extent, functional MRI studies have often investigated specific brain regions of interest, and as such could have failed to detect effects of stimulant treatment on other regions. Finally, signs of considerable publication bias have been reported in clinical treatment literature, where null-findings or conflicting findings are less likely to be published (Dwan et al., 2008; McGauran et al., 2010). We cannot exclude the possibility that a similar issue may be at play in the literature on brain changes induced by methylphenidate and as such may limit our understanding of its effects.

A number of issues are of great importance for future work. First, an unresolved issue is the link between structural and functional brain changes induced by methylphenidate treatment on the one hand, and clinical response to methylphenidate treatment on the other. Not all children with ADHD respond to stimulant treatment in the same way, both at the neural and behavioral level. One promising approach would be to compare responders to non-responders. This could provide researchers with valuable clues as to which regions or processes in the brain are related to the beneficial effects to stimulant treatment.

Secondly, the long-term effects of stimulant treatment on the brain functioning are largely unknown. The long-term normalizing effects of stimulant treatment on brain structure in children with ADHD, appear paradoxical to the rapid return of ADHD symptoms after stimulant treatment is ceased, and do not correspond with the putative evidence of the absence of long-term functional brain changes with stimulant treatment. In future studies, a developmental perspective will be critical, since brain development may well add to the existing variability in methylphenidate-induced brain changes in children with ADHD. Moreover, long-term methylphenidate effects may become apparent only after adolescence or young adulthood, when neurodevelopment enters a more stable phase (Andersen, 2005). Long-term effects of methylphenidate treatment on the developing brain should ideally be investigated in a large prospective cohort of children with ADHD as well as typically developing control subjects, with both structural and functional neuroimaging sessions before stimulant treatment is initiated, and follow-up continuing into adulthood.

MR imaging of methylphenidate effects could benefit from adding genetic markers to relate to individual differences in treatment response. Neuroimaging of the effects of methylphenidate could serve as an endophenotype between genetic predisposition and clinical amelioration with methylphenidate treatment, by comparing methylphenidate-induced alterations in brain functioning and behavior between groups that differed in genotype for genetic polymorphisms relevant to

ADHD. Such an approach may relate the molecular basis of the clinical effects of the treatment, to neurobiological substrate of ADHD. In addition, such studies may provide geneticists with valuable biological markers in pursuit of identifying genes involved in brain structure and function in ADHD (Wood & Neale, 2010). Several promising papers have appeared combining pharmacogenetics with neuroimaging methods other than MRI, such as SPECT and EEG (e.g., Loo et al., 2003; Rohde et al., 2003).

In sum, a modest literature suggests that the effects of methylphenidate treatment on brain development in ADHD are highly specific and dependent on numerous factors, including biological factors such as genetic predispositions, subject-related factors such as age and symptom severity, and task-related factors such as task difficulty. Future studies on structural and functional brain changes in ADHD would benefit from inclusion strategies guided by current medication status and medication history and will need to address unresolved issues including the effects of the long-term treatment, and the mechanism underlying its therapeutic effects.