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Review

Impulsiveness as a timing disturbance: neurocognitive abnormalities in attention-deficit hyperactivity disorder during temporal processes and normalization with methylphenidate

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We argue that impulsiveness is characterized by compromised timing functions such as premature motor timing, decreased tolerance to delays, poor temporal foresight and steeper temporal discounting. A model illustration for the association between impulsiveness and timing deficits is the impulsiveness disorder of attention-deficit hyperactivity disorder (ADHD). Children with ADHD have deficits in timing processes of several temporal domains and the neural substrates of these compromised timing functions are strikingly similar to the neuropathology of ADHD. We review our published and present novel functional magnetic resonance imaging data to demonstrate that ADHD children show dysfunctions in key timing regions of prefrontal, cingulate, striatal and cerebellar location during temporal processes of several time domains including time discrimination of milliseconds, motor timing to seconds and temporal discounting of longer time intervals. Given that impulsiveness, timing abnormalities and more specifically ADHD have been related to dopamine dysregulation, we tested for and demonstrated a normalization effect of all brain dysfunctions in ADHD children during time discrimination with the dopamine agonist and treatment of choice, methylphenidate. This review together with the new empirical findings demonstrates that neurocognitive dysfunctions in temporal processes are crucial to the impulsiveness disorder of ADHD and provides first evidence for normalization with a dopamine reuptake inhibitor.

Keywords: impulsiveness; timing; time perception; temporal discounting; attention-deficit hyperactivity disorder; methylphenidate

1. IMPULSIVENESS IS DEFINED BY PROBLEMS WITH TIMING FUNCTIONS

Dictionary definitions of impulsiveness include terms such as 'acting without thinking', 'on the spur of the moment' and 'in brief intervals of time'. Psychologists define impulsiveness as a lack of persistence, reduced decision time and increased threshold for boredom (Buss & Plomin 1975), lack of patience, risk, sensation and seeking (Eysenck 1993), lack of 'futuring'/temporal foresight (Barrat 1994) and resistance to delayed rewards (Logue 1995). We have defined impulsiveness as a poorly controlled and inappropriately timed, usually premature, non-reflected, immediateness-bound and delay-aversed response style where actions are executed before all available information and the future consequences are being considered (Rubia 2002). It becomes obvious from these definitions of impulsiveness that abnormalities in functions of timing are an essential component of it.

'Prematurity', 'acting in brief intervals of time', 'reduced decision time' and 'acting on the spur of the moment, without thinking', for example, refer to the execution of acts at an inappropriately early moment in time, reflecting poor motor timing and underuse of reflection time. 'Present boundedness' or 'poor futuring' indicates insufficient use of inter-temporal bridging/temporal foresight. 'Risk taking and sensation seeking' reflect temporal myopia or poor consideration of the negative future consequences of such behaviours. 'Lack of persistence and resistance to delayed rewards' refer to steeper temporal discounting, i.e. the subjective devaluation of reward in proportion to its delay in time. Steeper temporal discounting is presumed to reflect shorter tolerance of temporal delays and enlarged subjective perception of time. A reduced tolerance to the passage of time is also reflected in other definitions such as 'lack of patience' and 'increased thresholds of boredom'.

In this paper, we argue that abnormalities in timing functions are fundamental to impulsiveness. Accordingly, impulsiveness manifests in abnormalities in different timing functions within different temporal

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domains that can be classified into the following neuropsychologically measurable subcomponents:

(i) *Motor timing*. Impulsive timing of behaviour is characterized by a premature and inconsistently paced response style. In the laboratory, motor timing is typically measured in tests of sensorimotor synchronization or anticipation in the milliseconds or seconds range.
(ii) *Time perception*. The passage of time appears to be subjectively longer/more intolerable forimpulsive people, suggestive of an abnormal time sense. In neuropsychological settings, fine-temporal perception is measured in time discrimination of short intervals in the milliseconds or seconds range. Time estimation is measured in tasks of time production/reproduction or estimation of typically seconds' intervals.
(iii) *Temporal foresight and temporal discounting*. Intertemporal bridging seems diminished in impulsive people. Temporal foresight is the most difficult to measure timing function as it can only be measured indirectly; for example, in gambling tasks that require the subject to learn and consider the future consequences of immediate reward choices, in tasks of forward planning or in tasks of temporal discounting, all of which comprise larger temporal domains such as days, weeks, months and years. Temporal discounting measures the degree to which a reward is discounted in relation to its temporal delay, i.e. the subjective value of the temporal delay in terms of reward. It requires temporal foresight in order to assess the larger future gain against the smaller immediate gain. Poor temporal discounting reflects either a dislike of temporal delay, probably due to an enlarged time sense, or reduced temporal foresight, or both.

We do not claim that *all* impulsiveness features can be accounted for by poor timing functions. We have previously argued that besides timing functions, problems with self-control functions, manifesting in poor inhibitory and attention functions are also key ingredients to impulsiveness (Rubia 2002). Timing, attention and inhibitory functions are in fact closely interrelated in behavioural as well as neuropsychological datasets (Olson *et al.* 2007; Rubia *et al.* 2007*a*), and appear to be different aspects of a multifaceted construct of impulsiveness (Reynolds *et al.* 2008). Most timing functions furthermore co-measure other cognitive basis functions depending on the temporal domains they cover. For example, attention to time is co-measured in many timing tasks, in particular estimation of longer intervals. Time reproduction relies on working memory functions and the ability to delay a response (inhibitory control), whereas psychophysical time discrimination tasks also tap into sensory processes.

Problems with reward and motivation have also been related to impulsiveness (Gray 1987). However, the most consistent association is with reduced sensitivity to reward delays, i.e. the timing of the reward, not the reward itself, reflecting hypersensitivity to the passage of time, not reward. It is not within the scope of this paper to discuss the inter-relationship between timing and these other functions that contribute to the complex construct of impulsiveness. The aim of this paper is to shape out—in our opinion—the underrated and underinvestigated timing aspects of impulsiveness. However, this does not reflect an exclusively reductionistic viewpoint and we acknowledge the importance of other aspects to impulsiveness, in particular inhibitory and attention functions.

2. DEFICITS IN TIMING FUNCTIONS IN IMPULSIVENESS AND ATTENTION-DEFICIT HYPERACTIVITY DISORDER

In support of the hypothesis that impulsiveness is essentially an abnormality of temporal processes, impulsiveness features have been associated with impairment in these different timing functions both in the normal and pathological populations. Thus, motor timing, time estimation and temporal foresight processes have been shown to be impaired in impulsive personalities (Van den Broek *et al.* 1992; Ostaszewski 1996; Reynolds & Schiffbauer 2004) and in adult impulsiveness disorders such as substance abuse (Reynolds 2006; Wittmann *et al.* 2007*a*,*b*), borderline personality disorder (Bazanis *et al.* 2002; Berlin *et al.* 2005) and mania (Bschor *et al.* 2004; Christodouiou *et al.* 2006). They are also impaired in patients with fronto-striatal brain lesions and secondary impulsiveness (Rubia *et al.* 1997; Bechara & Van der Linden 2005).

Attention-deficit hyperactivity disorder (ADHD) is the archetypal neurodevelopmental impulsiveness disorder. ADHD develops in childhood and is defined by age-inappropriate problems with hyperactivity, inattention and impulsiveness, with impulsiveness being the key feature (APA, DSM IV). All of the above given definitions of impulsiveness are met by the behavioural and cognitive manifestation of ADHD.

Only relatively recently, timing functions have been investigated in children with ADHD. These by and large support the hypothesis that timing problems in several temporal domains are characteristic of ADHD and correlate with their behavioural impulsiveness (Toplak *et al.* 2006).

One of the most consistent findings are deficits in the fine-temporal discrimination of intervals that differ by milliseconds and seconds (Smith *et al.* 2002; Toplak *et al.* 2003; Rubia *et al.* 2003*b*, 2007*a*). Within a large battery of executive function tasks, time discrimination deficits were the most sensitive group discriminator, correctly classifying over 70 per cent of cases and controls (Rubia *et al.* 2007*a*).

Although findings have been less consistent, overestimation and under(re)production of time intervals have also been observed, suggestive of a faster internal time sense, which correlated with behavioural impulsiveness in several studies (Toplak *et al.* 2006).

ADHD children are more inconsistent or erratic in synchronizing or anticipating their motor response to sensory stimulation (Rubia *et al.* 1999*a*, 2003*b*; Ben-Pazi *et al.* 2006). They also make consistently premature responses across tasks, reflecting a task-independent and ubiquitous deficit that has been considered an indirect indicator of poor motor timing

(Rubia *et al.* 2001, 2007*a*); after time discrimination errors, with which it was closely inter-correlated, it was one of the best discriminators between ADHD and controls among a range of neuropsychological measures (Rubia *et al.* 2007*a*).

Recent evidence also has pointed at problems with temporal foresight and temporal discounting of longer intervals. ADHD children show poor inter-temporal choice in gambling tasks, in correlation to their behavioural impulsiveness (Garon *et al.* 2006; Toplak *et al.* 2008) and have steeper temporal discounting (Luman *et al.* 2005).

It cannot be excluded, however, that the timing deficits observed in ADHD are related to other cognitive deficits. Problems with attention to time, working memory and inhibition of immediate responding, for example, rather than abnormalities with temporal processes *per se*, could well affect performance on timing tasks.

3. SIMILARITIES BETWEEN THE NEURAL CORRELATES OF TIMING FUNCTIONS AND THOSE OF ADHD

Interestingly, the neural correlates of those timing functions that are impaired in ADHD children are strikingly similar to the neural correlates of ADHD, further supporting the link between the two.

Several brain regions have been implicated in timing functions, including prefrontal and parietal cortices, the basal ganglia, the cerebellum, anterior cingulate gyrus (ACG) and supplementary motor area (SMA). Evidence from the literature suggests that each of these brain regions may contribute to specific aspects of timing functions (Rubia & Smith 2004; Rubia 2006; Wittmann 2009).

The cerebellum and the basal ganglia seem to be the closest in mediating pure timing mechanisms as they have been associated with motor and perceptive timing of both short and long temporal domains. The cerebellum is important for event timing and temporal prediction (Ivry *et al.* 2004). The basal ganglia show sustained activity during temporal intervals and have been suggested to play a role in sustained attention to time and inter-temporal bridging (Buhusi & Meck 2005; Koch *et al.* 2009).

Lateral prefrontal regions are particularly involved in timing processes that require the temporal bridging of longer temporal intervals, which has been linked to other functions that are known to be mediated by these regions such as sustained attention to time, delay of immediate responses, magnitude comparation and working memory (Koch *et al.* 2009; Lewis & Miall 2006).

The SMA and the ACG have traditionally been related to motor timing, although more recent evidence has showed they have a role in pure perceptual time estimation, necessary for fine-temporal adjustment of movement. The ACG and SMA via their close connections to fronto-striatal pathways may have a more generic role in attentional components necessary for both motor timing and time estimation in an evaluative comparator role (Macar *et al.* 2006; Rubia 2006).

The parietal lobes have been related to perceptual timing and temporal foresight of longer time domains, and are thought to support timing functions through the allocation of sustaining attention to time and their function as a number and magnitude comparator (Rubia 2006).

It thus appears that complex fronto-parieto-striato-cerebellar neural networks are involved in timing functions concerting efforts from these different brain regions that mediate basis functions that together compose complex temporal processes (Rubia 2006).

All these brain regions that are crucial to temporal processes are impaired structurally and functionally in ADHD. Structural imaging studies in children with ADHD have demonstrated abnormal brain volumes, a delayed development and reduced white matter integrity in the cerebellum, caudate, frontal, temporal and parietal lobes (Ashtari *et al.* 2005; Shaw *et al.* 2007; Valera *et al.* 2007).

Functional imaging studies show dysfunctions in the same brain regions during tasks of cognitive control, most consistently in the inferior prefrontal cortex, caudate and anterior and posterior cingulate (Rubia *et al.* 1999*b*, 2001, 2005*a*, 2007*b*, 2008, 2009; Smith *et al.* 2006) but also in temporo-parietal and cerebellar areas during attention tasks (Smith *et al.* 2006; Rubia *et al.* 2007*b*, 2009).

4. NEUROCOGNITIVE DYSFUNCTIONS IN ADHD DURING TIMING PROCESSES: MOTOR TIMING, TIME DISCRIMINATION AND TEMPORAL DISCOUNTING

To investigate our hypothesis that ADHD is associated with neurofunctional abnormalities of brain regions that mediate timing functions, we scanned adolescents with ADHD while performing several functional magnetic resonance imaging (fMRI)-adapted timing tasks of different temporal domains. In our first studies in 1999 and 2001, we investigated the neural correlates of sensorimotor synchronization to time intervals that either lasted 600 ms—measuring pure sensorimotor synchronization—or 5 s—requiring additional frontal lobe-mediated time estimation. Adolescents with ADHD showed no performance differences in the task and no brain dysfunctions during sensorimotor tapping to the short 600 ms interval (Rubia *et al.* 2001); however, they showed significant underfunctioning of the anterior and posterior cingulate during motor timing to the 5 s interval (Rubia *et al.* 1999*b*, 2001; figure 1*a*). In a subsequent study, we investigated the neural correlates of time discrimination of hundreds of millisecond differences from a base interval of 1 s in 21 medication-naive adolescents with ADHD compared with 17 control children. We found significantly reduced activation in the ADHD adolescents in brain regions, which correlated significantly with time discrimination performance in controls in right inferior and dorsolateral prefrontal cortices, the ACG and SMA (Smith *et al.* 2008; figure 1*b*).

In order to investigate the neural substrates of the tolerance of time and the use of temporal foresight in ADHD children, we conducted a third fMRI experiment using a task of hypothetical temporal discounting

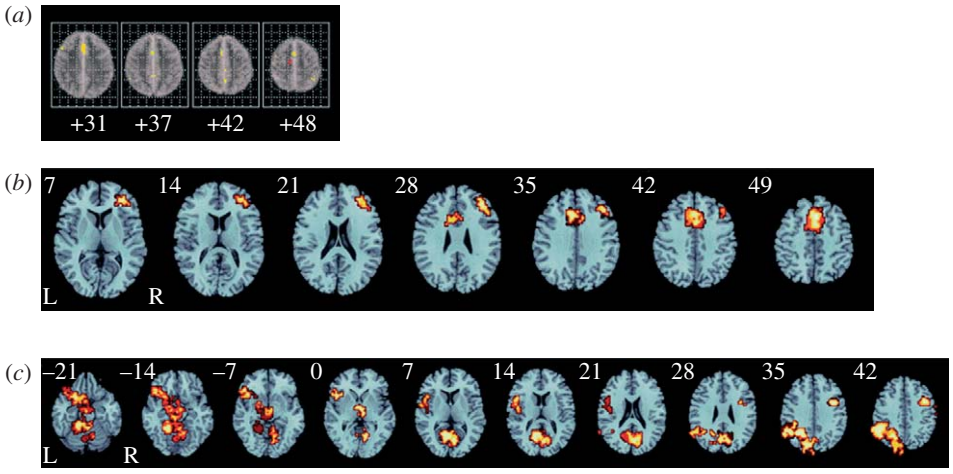

Figure 1. ANOVA between-group differences showing reduced brain activation in ADHD boys compared with healthy comparison boys. (*a*) Motor timing of 5 s, seven boys with ADHD compared with nine healthy controls during a sensorimotor synchronization task to a 5 s interval (Rubia *et al.* 1999*b*); (*b*) temporal discrimination of hundreds of millisecond differences, 21 medication-naive ADHD boys compared with 17 healthy controls during temporal discrimination of intervals that differed by hundreds of milliseconds (Smith *et al.* 2008); and (*c*) temporal discounting of a week, month and year, 10 boys with ADHD compared with 10 healthy controls during a temporal discounting task of weeks to a year.

of longer intervals of weeks to years in 10 adolescents with and without ADHD. The choice of delayed versus immediate rewards during delay discounting (DD) tasks has been associated with the activation of lateral prefrontal and parietal cortices (McClure *et al.* 2004), but also subcortical regions including the insula, basal ganglia and cerebellum, suggestive of a fronto-parieto-striato-cerebellar network for temporal discounting (Hariri *et al.* 2006; Wittmann *et al.* 2007*a*,*b*).

Given the evidence for steeper temporal discounting in ADHD children (Luman *et al.* 2005) and abnormalities in brain regions that mediate these functions (§3), we hypothesized that ADHD adolescents would show underactivation in task-relevant brain regions of lateral prefrontal and parietal cortices, basal ganglia and cerebellum (McClure *et al.* 2004; Hariri *et al.* 2006).

(a) *Method*

(i) *Subjects*

Patients

Ten male right-handed adolescent boys in the age range of 11–16 years (mean age = 14, s.d. = 2) with a clinical diagnosis of the combined inattentive–hyperactive subtype of ADHD were recruited through parent groups and clinics. Exclusion criteria were neurological abnormalities, epilepsy and substance abuse, co-morbidity with other major psychiatric disorders including language or learning problems, except for conduct disorder, met by one patient. Four patients were medication naive and the other six were taken off methylphenidate (MPH) for 36 hours prior to scanning. Patients scored above the cut-off for hyperactive symptoms on the strengths and difficulties questionnaire (SDQ; Goodman & Scott 2005).

Healthy controls

Ten male right-handed adolescent boys between 11 and 17 years (mean age = 15, s.d. = 4) were recruited through advertisements; they scored below the cut-off for behavioural problems on the SDQ and had no history of psychiatric disorder.

All participants achieved a score above 80 on the Wechsler abbreviated scale of intelligence (Wechsler 1999) (mean IQ controls = 119, s.d. = 7; patients = 109, s.d. = 9) and were paid £30 for participation. Parental and child informed consent/assent and approval from the local ethical committee were obtained.

Univariate ANOVAs showed no group differences in age ($F_{1,19} = 2$, p = n.s.), but IQ ($F_{1,19} = 7$; $p < 0.02$). IQ and age had no effect on the performance variables. Nevertheless, because controls differed in IQ and were on average a year older, all subsequent analyses were co-varied for both IQ and age.

(ii) *fMRI delay discounting task*

In the 12 min task, subjects choose by pressing a left or right button (with the right index or right middle finger) between a smaller amount of money (between £0 and £100), immediately, and a larger amount (always £100) after 1 week, 1 month or 1 year; choices were randomly displayed (20 trials for each delay) to the right and left sides of the screen for 4 s, followed by a blank screen of at least 8 s (inter-trial interval: 12 s). The immediate reward is adjusted in an algorithm based on previous choices for each of the three different delays to narrow the range of values converging into an indifference value that is considered by the subject as equivalent to the delayed reward (Richards *et al.* 1999). The algorithm ensures that equal numbers of immediate and delayed reward choices are obtained at the end of the task which are then contrasted in the fMRI analysis.

Reward is typically discounted in a hyperbolic function that depends on amount, delay and a free impulsiveness indicator k, the main dependent task variable that can be calculated by fitting a hyperbolic function to the indifference values for every delay. Larger k values are associated with greater reward devaluation (Richards *et al.* 1999).

(iii) *fMRI image acquisition and analysis*

fMRI images were acquired on a 3 T General Electric (GE) MRI scanner. In each of 22 non-contiguous

Table 1. Between-group ANCOVA differences in brain activation between controls and patients for the contrast of delayed–immediate responses during temporal discounting. (BA, Brodman area; *N* voxels, number of voxels; Tal. co-ordinates, Talairach coordinates. *p*-value for ANCOVAs at $p<0.05$ for voxel activation and $p<0.006$ for cluster activation. Those *p*-values were selected to yield less than 1 false positive cluster per brain map.)

brain region	BA	Tal. coordinates (*x*, *y*, *z*)	*N* voxels	cluster *p*-value
controls>ADHD				
L precuneus/posterior cingulate/cerebellum/brainstem/orbital/inferior/prefrontal/thalamus/putamen	7/31/11/47	−25, −56, 31	985	0.0008
orbitofrontal/inferior prefrontal gyrus[1]	*11/47/45*	*−40, 33, −24*		
inferior parietal lobe[a]	*40*	*−50, −58, 31*		
posterior cingulate[a]	*31*	*−25, −52, 26*		
cerebellum/brainstem[a]		*7, −40, −24*		
R inferior prefrontal gyrus	44	40, 7, 31	220	0.003

[a]Large three-dimensional clusters were broken into smaller two-dimensional clusters (see italics).

planes parallel to the anterior–posterior commissure, 480 T2-weighted MR images were acquired depicting blood oxygen level-dependent (BOLD) contrast with echo time (TE) = 30 s, repetition time (TR) = 1.5 s, 22 functional slices and functional slice thickness = 5.5 mm (superimposed on a high-resolution (3 mm) image of the whole brain).

Time-series analysis for each individual subject was based on a wavelet-based data resampling method for functional MRI data (Bullmore *et al.* 1999). Images were registered into Talairach standard space. A group brain activation map was then produced for each experimental condition and hypothesis testing was carried out at the cluster level, shown to give excellent cluster-wise type I error control in structural and functional fMRI analyses (Bullmore *et al.* 1999). For each task, less than 1 false-positive-activated cluster was expected at a *p*-value of <0.05 at the voxel and <0.02 at the cluster level. ANCOVA analysis for between-group differences was conducted using randomization-based test for voxel or cluster-wise differences (Bullmore *et al.* 1999). Less than 1 false-activated cluster was expected at a *p*-value of $p<0.05$ for voxel and $p<0.006$ for cluster comparisons.

(b) *Results*

(i) *Task performance*

Discounting followed the typical hyperbolic function. Univariate ANCOVAs showed no group differences for the main impulsiveness factor k (controls mean $k=0.015$, s.d. = 0.012; ADHD means $k=0.034$, s.d. = 0.048, $F_{1,19}=0.1$, p = n.s.); larger k was positively correlated with higher SDQ hyperactivity scores ($r=0.4$, $p<0.04$). However, there was a larger reaction time effect for delayed choices compared with immediate choices for controls (i.e. delayed choice RT effect (RT delayed–RT immediate): controls mean = 178 ms, s.d. = 159 ms; ADHD mean = 11 ms, s.d. = 373 ms, $F_{1,19}=5$, $p<0.036$), suggesting that controls, but not ADHD, deliberated longer when choosing delayed over immediate rewards.

(ii) *Brain activation for delayed–immediate choices*

Controls activated bilateral cerebellum, posterior cingulate/precuneus and parietal lobe. Boys with ADHD activated insula, SMA, premotor cortex and parietal lobes.

ANCOVA showed increased activation for controls compared with ADHD boys in two clusters; one comprising left orbital and inferior prefrontal cortices, putamen, thalamus, inferior parietal lobe, posterior cingulate/precuneus and cerebellum; and the other in the right inferior prefrontal cortex (table 1; figure 1). Activation in both group difference clusters correlated significantly negatively with the hyperactivity measures on the SDQ ($r=0.6$, $p<0.005$). The activation in cerebellum correlated positively with the delayed choice RT effect ($r=0.5$, $p<0.013$). ADHD compared with control boys showed no increased activation.

(c) *Discussion*

Although ADHD children had steeper discounting values that correlated with behavioural symptoms, this did not reach significance. This is probably due to the small number of subjects for neuropsychological data and the older age group tested in this fMRI study compared with the younger populations that have previously shown to have deficits in the task (Luman *et al.* 2005). However, ADHD children deliberated significantly less than control boys over delayed compared with immediate reward choices, suggesting a decreased use of inter-temporal bridging time and thus presumably less foresighted delayed reward choices.

In the fMRI data, ADHD boys showed significantly reduced activation in left and right inferior prefrontal and left lateral orbitofrontal cortices, as well as in left thalamus, putamen, cerebellum, inferior parietal lobe and posterior cingulated/precuneus. As mentioned above, ventrolateral fronto-parieto-striato-cerebellar brain regions are typical areas of temporal discounting (McClure *et al.* 2004; Hariri *et al.* 2006; Wittmann *et al.* 2007*a*,*b*) as well as key areas of dysfunction in ADHD children during tasks of inhibition and attention (Rubia *et al.* 1999*b*, 2005*a*, 2007*b*, 2008, 2009). It is likely that these ventrolateral fronto-parieto-striato-cerebellar networks that are compromised in ADHD are mediating several component functions that are necessary for temporal foresight. The orbitofrontal cortex, for example, is thought to be important for holding information in representational memory as well as incentive motivation, and is thus crucial for comparator operations of future and current rewards (Schoenbaum *et al.* 2006). Inferior prefrontal

activation is inversely associated with the steepness of DD in adults (Wittmann *et al.* 2007*a*,*b*) but also mediates closely related functions of sustained attention, inhibition and working memory (Rubia *et al.* 2003*a*, 2006, 2007*c*, 2009); these functions may contribute to delayed gratification, which involves the inhibition of the immediate reward as well as attention to and holding online of the future reward perspective. The inferior prefrontal dysfunction is a key finding in ADHD in the context of millisecond time discrimination (Smith *et al.* 2008) as well as non-timing cognitive control functions (Rubia *et al.* 1999*b*, 2005*a*, 2008, 2009). Furthermore, both the right inferior prefrontal as well as the left fronto-striato-cerebellar dysfunctions correlated with the behavioural hyperactivity measures. The inferior parietal regions are important for allocating attention to time, imagery and quantity representations, and may thus contribute to inter-temporal choice in their role as magnitude comparators of both time and reward (Sandrini *et al.* 2004). The posterior cingulate mediates visual–spatial attention to reward (Small *et al.* 2003) and delay gratification (Wittmann *et al.* 2007*a*,*b*), and was also reduced in ADHD children during rewarded attention trials (Rubia *et al.* 2009) and may thus reflect reduced attentional representation of the delayed reward option. The putamen is important for attention to time, in particular when comparing long with short intervals (Rubia *et al.* 1998; Coull *et al.* 2004). As mentioned, the cerebellum is a key area for both long and short interval timings and was the only region that correlated positively with the delayed RT choice effect, suggesting that this region may be instrumental in the temporal perspective of the expected delayed gratification. The functional interplay between these different brain regions may thus provide the combination of skills that are necessary to compare and then make an informed decision for delayed gratification. The reduced recruitment of this ventrolateral fronto-striato-cerebellar network in ADHD adolescents during delayed gratification choices combined with the reduced use of reflection time—a typical impulsiveness feature—may be the neural substrate for the typically observed reduced temporal foresight mechanisms in ADHD.

To summarize, these three fMRI studies demonstrate that ADHD children have task-relevant brain dysfunctions during different temporal processes, motor timing, time discrimination and temporal discounting, covering three different temporal domains. Brain dysfunctions were in anterior cingulate during motor timing of seconds and millisecond time discrimination, presumably reflecting attention to time; in right lateral prefrontal cortex during time discrimination and temporal discounting of longer intervals, an area thought to mediate time estimation; and in a left ventrolateral fronto-parieto-striato-thalamo-cerebellar network during temporal discounting, presumably mediating temporal foresight. These brain regions are key areas of functional and structural brain abnormalities in ADHD, also during inhibition and attention, which may interact with timing abnormalities to provide the complex construct of impulsiveness.

5. PSYCHOSTIMULANTS AND EFFECTS ON TIMING

Dopamine is the neurotransmitter that has most consistently been implicated in timing functions. Dopaminergic agonists/antagonists are known to improve/deteriorate time estimation, motor timing and temporal discounting in humans (Rammsayer 1993; Takahashi 2007) and animals (Buhusi & Meck 2005).

Given that timing processes of longer intervals of several seconds co-measure other than pure timing functions, such as working memory, attention to time, magnitude estimations and the ability to inhibit immediate responses, several neurotransmitters besides dopamine including noradrenergic, serotoninergic, GABAergic and glutamatergic systems have also been involved in these functions (Rammsayer *et al.* 2001; Rammsayer 2003). Shorter subsecond time-interval timing, however, appears to be more specifically modulated by dopaminergic activity (Rammsayer & Stahl 2006).

ADHD is thought to be mediated by a dopamine dysfunction; there is consistent evidence for elevated striatal dopamine transporter levels and reduced DA availability (Krause 2008). A dopamine dysfunction is likely to account for their deficits in timing functions.

The psychostimulant MPH is the most effective, first choice treatment for the behavioural symptoms of ADHD (Arnsten 2006). However, little is known on its mechanisms of action. MPH is a catecholamine reuptake inhibitor with stronger dopaminergic effects subcortically (Arnsten 2006).

Neuropsychological studies show that MPH improves abnormal timing functions in ADHD children. We found that chronic MPH administration over a month improved speed, errors and intra-subject variability of sensorimotor synchronization and anticipation (Rubia *et al.* 2003*a*). Acute doses of MPH have been shown to increase precision of subsecond synchronization (Ben-Pazi *et al.* 2006), of time estimation of several seconds (Baldwin *et al.* 2004) and to improve inter-temporal choice in gambling tasks in patients with ADHD (DeVito *et al.* 2008).

6. NEW DATA: EFFECTS OF MPH ON BRAIN DYSFUNCTION IN ADHD DURING TIME DISCRIMINATION

Relatively, few fMRI studies have studied the effects of MPH on brain activation in ADHD, finding enhanced activation in the caudate and ACG (Vaidya *et al.* 1998; Shafritz *et al.* 2004). However, no fMRI study so far has investigated temporal processes.

In order to investigate the effects of MPH on timing functions in ADHD, we conducted a double-blind, randomized, placebo-controlled fMRI experiment in 12 medication-naive boys with and without ADHD while they performed a task of time discrimination. We investigated (i) the effects of MPH compared with placebo within patients and (ii) potential amelioration or normalization effects of MPH on brain dysfunctions in comparisons between controls and patients under either placebo or medication.

Given the evidence for dopamine involvement in subsecond time discrimination (Rammsayer 1993;

Table 2. Within-patients ANOVA differences in brain activation between the MPH and the placebo conditions during time discrimination versus order judgement. (BA, Brodman area; *N* voxels, number of voxels; Tal. co-ordinates, Talairach coordinates. *p*-value for ANCOVAs at $p<0.05$ for voxel activation and $p<0.006$ for cluster activation.)

brain region	BA	Tal. coordinates (*x*, *y*, *z*)	*N* voxels	cluster *p*-value
(*a*) *methylphenidate > placebo*				
L orbitofrontal/inferior frontal gyri/insula	47/45	−33, −11, −2	419	0.002
R medial prefrontal gyrus[a]	*46*	*40, 44, 9*	*38*	*0.02*
L anterior cingulated gyrus[a]	*32*	*−6, 37, 26*	*35*	*0.03*
R lateral cerebellum[a]		*14, −52, 46*	*30*	*0.05*
(*b*) *placebo > methylphenidate*				
R inferior/medial frontal gyri/insula	9/8/44	25, 15, 28	25	0.002
R superior frontal gyrus	8	18, 30, 49	14	0.003
R medial temporal lobe	22	29, −33, 7	23	0.002
R hippocampus, hippocampal gyrus	35	22, −15, −7	41	0.002
R putamen and globus pallidus	11	29, −11, 7	11	0.002

[a] Large three-dimensional clusters were broken into smaller two-dimensional clusters.

Rammsayer & Stahl 2006), we used a discrimination task of temporal differences of hundreds of milliseconds which has shown to elicit deficits in ADHD children (Smith *et al.* 2002; Rubia *et al.* 2007*a*). The task activates key timing regions of right dorsolateral and inferior prefrontal cortices, the cerebellum, ACG and the SMA in adults and children (Smith *et al.* 2003, 2008), and elicits underactivation in ADHD adolescents in right lateral prefrontal cortex, ACG and SMA (§3; figure 1*b*; Smith *et al.* 2008). We hypothesized that we would replicate our previous findings of fronto-cingulate underactivation in ADHD adolescents during the placebo condition and, furthermore, that MPH would ameliorate or normalize the activation differences between patients and controls.

(a) *Method*

(i) *Subjects*

Twelve male right-handed adolescent boys in the age range of 10–15 years (mean age = 13, s.d. = 1), who met clinical diagnostic criteria for the combined, inattentive–hyperactive subtype ADHD (DSM-IV), were recruited through clinics. All the patients were medication naive. Exclusion criteria were co-morbidity with other major psychiatric disorders except for conduct disorder (one patient), with language and learning disabilities, neurological abnormalities, drug or substance abuse. Patients with ADHD scored above cut-off for hyperactive symptoms on the SDQ (Goodman & Scott 1999).

The patients were scanned twice, in a randomized fashion, one week apart, 1 hour after either $0.3\ \mathrm{mg\ kg^{-1}}$ of MPH administration or placebo (vitamin C, 100 mg).

Twelve male right-handed adolescent boys in the age range of 11–16 years (mean age = 13, s.d. = 1) were recruited through advertisements. They scored below the cut-off for the SDQ, and had no history of psychiatric disorder.

All the participants were above the fifth percentile on the Raven progressive matrices performance IQ (Raven 1960; IQ mean estimate controls = 100, s.d. = 14; ADHD = 91, s.d. = 9) and were paid £30 for participation. Parental and child informed consent/assent and approval from the local Ethical Committee were obtained.

Univariate ANOVAs showed no group differences between children with ADHD and controls for IQ ($F_{1,23}=0.8$, p = n.s.) or age ($F_{1,23}=4$, d.f. = 1, p = n.s.).

(ii) *fMRI time discrimination task*

The block design time discrimination task consisted of 5 × 30 s alternated blocks for each condition (six trials each). In the time discrimination blocks, starting with the appearance of a cue letter 'L' for 3 s, a pair of differently coloured circles was presented consecutively left and right from each other. One of these circles was randomly presented for a standard duration of 1000 ms, and the comparison circle for 1300, 1400 or 1500 ms. Subjects had to decide which of the two circles had the longer duration by pressing either the left or right button (left/right thumb). The temporal order judgement (control) condition was identical to the time discrimination condition except that these blocks began with the presentation of the cue number '2' and subjects had to indicate which circle came second. For the fMRI analysis, activation during the control condition was subtracted from activation during the time discrimination condition (Smith *et al.* 2003, 2008).

(iii) *fMRI data acquisition and analysis*

fMRI images were acquired on a 1.5 T GE MR scanner. In each of 16 non-contiguous planes parallel to the anterior–posterior commissure, 100 T2-weighted MR images depicting BOLD contrast were acquired with TE = 40 ms; TR = 3 s; flip angle 90°; 64 × 64 matrix; in-plane voxel size 3.75 × 3.75 mm; slice thickness = 7 mm, slice skip = 0.7 mm. A high-resolution structural scan of 128 axial slices was acquired after the functional series.

Individual and group analyses were as described in §4. For group activations, less than 1 false-activated cluster was expected at a *p*-value of <0.05 for voxel and <0.01 for cluster comparisons. Three ANOVA analyses were conducted as described in §4. To test for a within-group effect of MPH versus placebo, a within-group repeated-measures ANOVA was conducted. To test for normalization effects, two ANOVAs were conducted: one between controls and patients under the placebo condition and the second one between controls and patients under the MPH

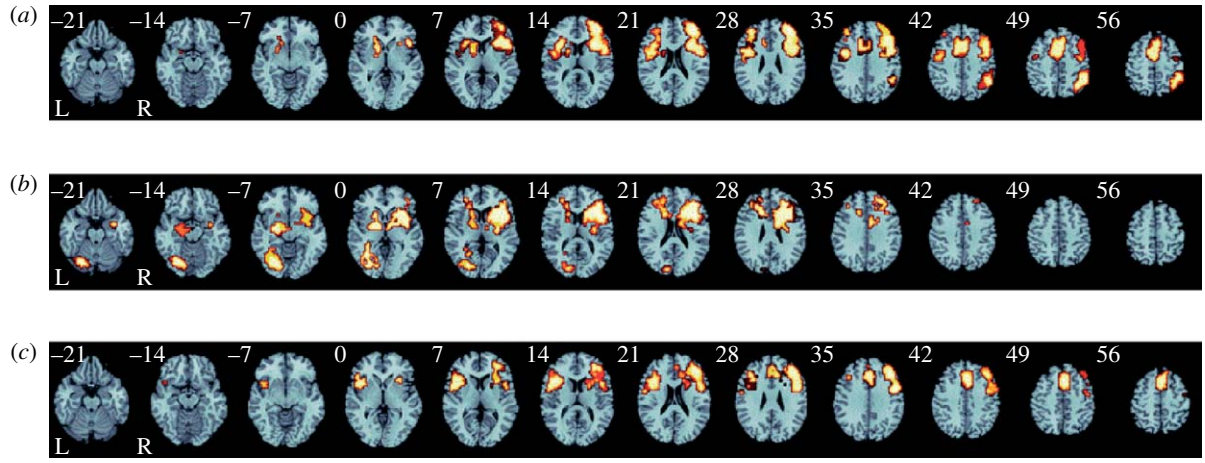

Figure 2. Within-group brain activation maps for the contrast of temporal discrimination versus order attribution task at $p<0.05$ for voxel and $p<0.01$ at cluster levels for (*a*) 12 healthy controls; and 12 medication-naive patients with ADHD under either (*b*) the placebo, or (*c*) the medication conditions.

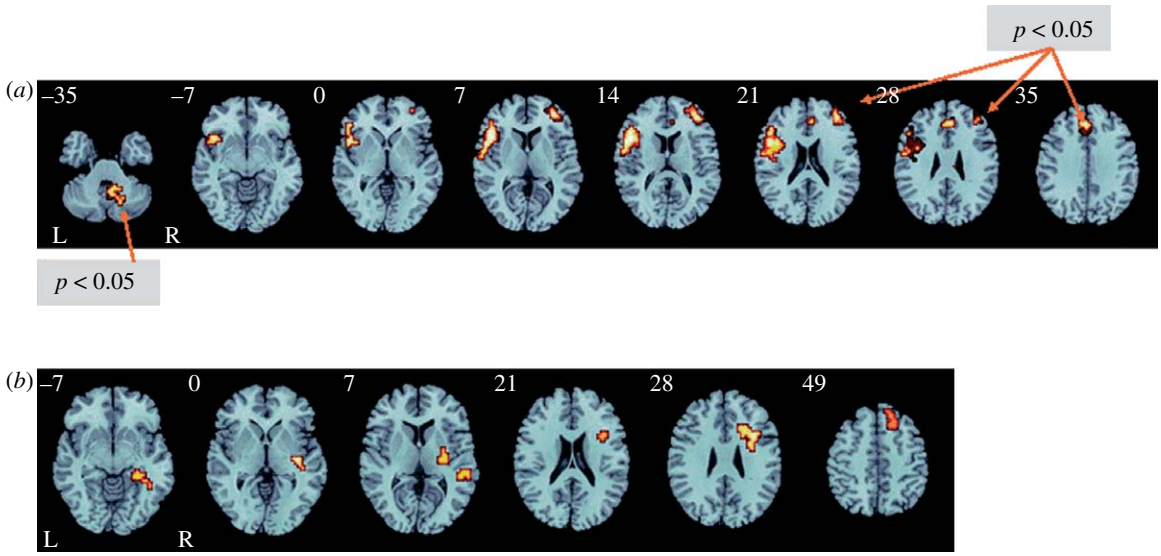

Figure 3. Within-group ANOVA comparing medication status for the time discrimination two-order attribution contrast at $p<0.05$ for voxel and $p<0.01$ for cluster levels. More lenient effects of MPH compared with placebo are also shown at $p<0.05$. (*a*) MPH > placebo and (*b*) placebo < MPH.

condition. Less than 1 false-activated cluster was expected at a *p*-value of <0.05 for voxel and <0.01 for cluster comparisons. To adjust for multiple testing, we used a more lenient threshold of $p<0.006$. A more lenient *p*-value of <0.05 was used to test for hypothesized subthreshold medication effects.

(b) *Results*

(i) *Performance*

Although the error rates in ADHD children were smaller during the MPH condition, this did not reach significance in the within-subject repeated measures ANOVA analysis ($F_{1,11}=0.3$, $p=$n.s.). Between-group ANOVAs showed no group differences between controls and ADHD patients under the placebo ($F_{1,23}=1$, $p=$n.s.) or MPH conditions ($F_{1,23}=1.4$, $p=$n.s.; error rates: controls: mean = 18%, s.d. = 17%; ADHD placebo: mean = 24%, s.d. = 17%; ADHD MPH: mean = 16%, s.d. = 22%).

(ii) *Brain activation*

Within-group activations for the contrast of time discrimination–order judgement are shown in figure 2 for controls (figure 2*a*), and for ADHD patients under the placebo (figure 2*b*) or the MPH condition (figure 2*c*). In all subjects activation was observed in dorsolateral and inferior prefrontal cortices, ACG and SMA, left caudate and insula.

Repeated-measures ANOVA within patients showed that MPH compared with placebo increased brain activation in a left hemispheric cluster in orbital and inferior prefrontal cortices. At a more lenient threshold ($p<0.05$), MPH also increased right dorsolateral prefrontal cortex, right cerebellum and ACG (table 2*a*; figure 3*a*).

Placebo compared with the MPH condition enhanced activation in patients in right hemispheric medial and superior frontal gyri, medial temporal lobe, hippocampus and lentiform nucleus (table 2*b*; figure 3*b*).

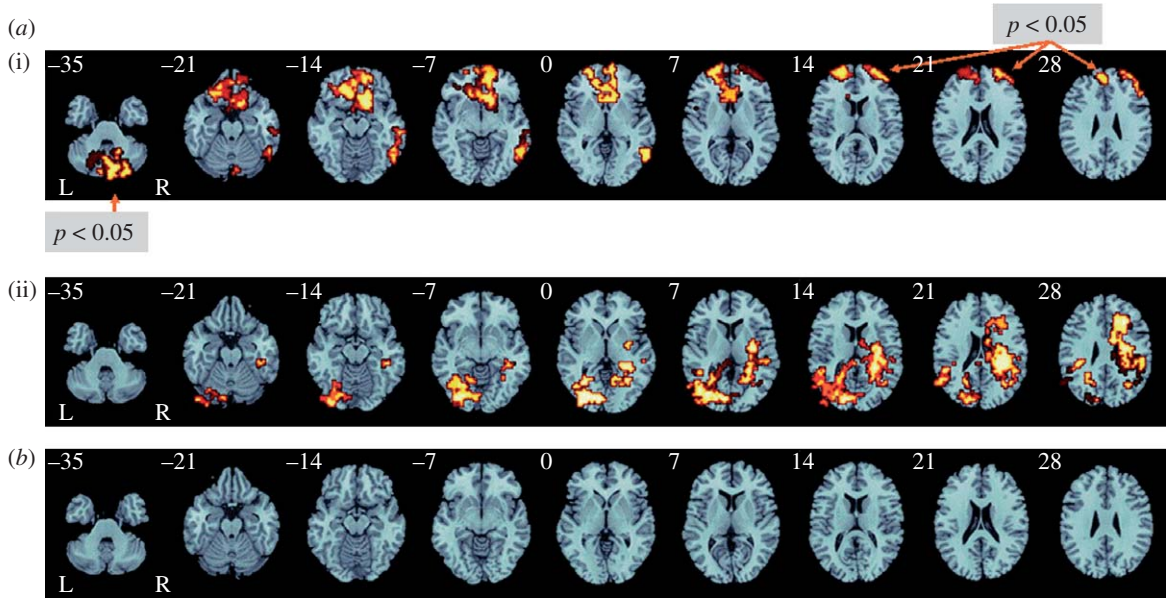

Figure 4. Case-control ANOVAs comparing healthy controls with ADHD boys for the contrast of time discrimination versus order attribution task during either the (*a*) placebo condition ((i) controls > ADHD and (ii) ADHD > controls) or (*b*) the medication condition (MPH) at $p < 0.05$ for voxel and $p < 0.006$ for cluster comparisons. Differences at more lenient *p*-values of < 0.05 at cluster levels are shown in (*a*).

Table 3. Between-group ANOVA differences in brain activation between controls and patients under the placebo condition for the contrast of time discrimination versus order judgement. (BA, Brodman area; *N* voxels, number of voxels. *p*-value for ANCOVAs at $p < 0.05$ for voxel activation and $p < 0.006$ for cluster activation.)

brain region	BA	Tal. coordinates (*x*, *y*, *z*)	*N* voxels	cluster *p*-value
(*a*) *controls > ADHD*				
R+L orbitofrontal/inferior/mesial frontal/ anterior cingulated/caudate	47/11/45/10/32/24	15, 19, −18	453	0.002
R inferior/medial frontal gyrus[a]	*44/46*	25, 59, 15	*42*	*0.04*
L anterior cingulate gyrus[a]	*32*	*−3, 55, 20*	*20*	*0.05*
R cerebellum[a]		*12, −73, −35*	*72*	*0.03*
(*b*) *ADHD > controls*				
L middle/superior temporal/occipital/ cerebellum	21/39/22/19/18	−43, −44, −2	502	0.002
R dorsomedial frontal/superior temporal/ insula/hippocampus/putamen	46/22/24/32	33, 26, 15	490	0.003

[a]Clusters that were significant at a more lenient *p*-value of < 0.05.

ANOVA comparison between controls and patients under the placebo condition showed increased activation in controls compared with patients for the contrast of time discrimination–order judgement in bilateral orbitofrontal cortex, caudate and ACG. At a more lenient threshold ($p < 0.05$), there was also increased activation in right cerebellum, right dorsolateral prefrontal cortex and a more dorsal part of ACG (table 3*a*; figure 4*a*). Activation in dorsal ACG furthermore correlated with time estimation errors in all subjects ($r = -0.4$, $p < 0.03$).

Patients compared with controls showed enhanced activation in two large clusters, comprising left temporal and occipital regions, and right superior temporal and inferior occipital regions reaching into dorsomedial frontal cortex (table 3*a*; figure 4*a*).

ANOVA comparison between controls and patients under the MPH condition revealed no significant differences, even at a more lenient cluster *p*-value of < 0.01 (figure 4*b*).

(c) *Discussion*

Despite non-significant differences in task performance, ADHD compared with control boys showed decreased activation during time discrimination in bilateral orbital, inferior and mesial prefrontal cortices, and caudate and enhanced activation in predominantly posterior regions of temporal lobes, thalamus and putamen. Within patients, MPH did not significantly increase performance, but enhanced activation in left inferior and right dorsolateral prefrontal cortices, ACG and cerebellum. MPH completely normalized all group activation differences that were observed under the placebo condition.

Despite the fact that the group differences and changes in performance elicited with MPH were in the right direction (reduced error rates in ADHD patients at baseline which were increased with MPH), they did not reach significance. This may be due to the relatively low statistical power for neuropsychological data and the use of an older adolescent age group compared

with the childhood age groups, previously shown to have time- discrimination deficits (Smith *et al.* 2002; Rubia *et al.* 2007*a*). The findings show that brain activation is more sensitive than performance to detect abnormalities and pharmacological effects. We have previously shown that adolescents with ADHD show marked brain dysfunctions despite not being significantly impaired in task performance (Rubia *et al.* 1999*b*, 2001, 2005*a*, 2008, 2009), even during the same time discrimination task (Smith *et al.* 2008; §4). We have also shown that the brain is more sensitive than behaviour to show pharmacological effects (Rubia *et al.* 2005*b*). However, some of the reduced activation clusters in ADHD patients which were normalized with stimulants correlated negatively with error rates, thus reinforcing the relationship between reduced brain activation and (albeit non-significantly) lower performance.

The underactivation in right prefrontal cortex and ACG under a more lenient threshold replicates our previous findings in a different group of 21 ADHD patients during the same task (§4; figure 1*b*; Smith *et al.* 2008). ACG was the only region that correlated with time estimation errors. The ACG underactivation in ADHD children was furthermore observed during motor timing to a 5 s interval (figure 1*a*). As discussed in §3, the ACG has consistently been implicated in timing functions of several temporal domains and is likely to mediate important basis functions that are necessary for timing processes such as attending, monitoring and comparing time intervals (Rubia *et al.* 1998; Rubia 2006).

The statistically more powerful dysfunction in bilateral ventromedial orbitofrontal cortex and the caudate as well as the subthreshold underactivation in the cerebellum was not observed in our previous study (figure 1*b*). As reviewed in §3, however, inferior/orbitofrontal cortex, ACG, caudate and cerebellum are key areas of structural and functional abnormalities in ADHD as well as key mediators of time discrimination (Smith *et al.* 2003, 2008). Furthermore, we also observed orbitofrontal dysfunction in ADHD adolescents during the temporal discounting task, albeit more laterally, together with reduced cerebellum and putamen activation (figure 1*c*). Lesion studies have attributed an important role to orbitofrontal cortex and its striatal connections in both temporal foresight of longer intervals as well as time estimation and discrimination of shorter time spans (Rubia *et al.* 1997; Bechara & Van der Linden 2005), possibly linked to its role in holding information in representational memory (Schoenbaum *et al.* 2006), important for the comparison of both long and short time intervals. The cerebellum plays an important role in millisecond discrimination (Smith *et al.* 2003, 2008; Rubia 2006). It is interesting that a similar location of the lateral cerebellum as well as the vermis was reduced during both temporal discounting and time discrimination, in line with the role of the cerebellum in the timing of both shorter and longer intervals (Rubia & Smith 2004; Rubia 2006). The cerebellum is the most compromised brain structure in ADHD (Valera *et al.* 2007) and a functional abnormality during short and long interval timing processes could be the underlying neural substrate for several impulsiveness-related timing deficits.

Within patients, MPH primarily enhanced left orbital/inferior prefrontal activation, but at a more lenient threshold also the ACG and right lateral prefrontal cortex, which were dysfunctional during placebo. As mentioned before, inferior prefrontal dysfunction is the most consistent fMRI finding in ADHD during tasks of inhibition and attention (§4), and even appears to be a specific biomarker for ADHD when compared with related pathologies such as conduct disorder (Rubia *et al.* 2008, 2009). The fact that inferior prefrontal dysfunction was also observed in other ADHD samples during the same task and during temporal discounting (§5; Smith *et al.* 2008; figure 1*b*,*c*) suggests that this brain dysfunction in ADHD may not only account for their poor attention and inhibitory control, but also be instrumental to their timing deficits. The inferior prefrontal cortex depending on its functional interconnectivities is important for many higher cognitive functions, and a localized dysfunction in this region in ADHD could account for the different deficits in the interrelated functions of attention, inhibition and timing. The MPH-induced enhancement and normalization of this consistently reported and potentially disorder-specific brain dysfunction in the context of timing could be associated with the disorder-specific effectiveness of MPH on ADHD-impulsive behaviours.

To our knowledge, this is the first functional imaging study that demonstrated (i) increased activation with MPH in ADHD patients in the most consistent dysfunction area, the inferior prefrontal cortex, and (ii) complete normalization of all brain activation abnormalities. Few functional imaging studies have included healthy controls to test for normalization effects of MPH. Only one of these studies found normalization of activation, but only in the caudate (Shafritz *et al.* 2004), while another study showed enhanced, but not normalized, activation in caudate and frontal regions (Vaidya *et al.* 1998). Not even chronic MPH administration over four weeks could show complete normalization of prefrontal and subcortical functions during attention tasks (Konrad *et al.* 2007; Bush *et al.* 2008). The normalization findings in ACG, inferior prefrontal cortex, caudate and cerebellum—key regions of both time discrimination and ADHD dysfunction (§4)—reinforce the association between dopaminergic neurotransmission abnormalities, ADHD and timing. While the effects on the caudate were probably mediated by the dopaminergic system (Krause 2008), the effects on frontal, cingulate and cerebellar brain regions, however, could also have been influenced by noradrenaline reuptake inhibition (Arnsten 2006).

In conclusion, this study shows that MPH has a complete normalization effect on brain dysfunctions in ADHD children in key areas of fine-temporal perception such as orbital and inferior prefrontal cortices, the caudate, ACG and cerebellum. Complete normalization with MPH on brain dysfunction has not been observed in any of the other disorder-relevant cognitive tasks of inhibition and attention (Vaidya *et al.* 1998; Shafritz *et al.* 2004), which suggests that MPH

may impact more prominently on neurocognitive abnormalities of timing functions, in line with the implication of DA in both timing and ADHD.

7. OVERALL CONCLUSIONS

In this paper, we claim that impulsiveness is essentially a problem of poor timing functions. We illustrate this in the classical neurodevelopmental impulsiveness disorder of ADHD. We review evidence that children with ADHD have deficits in timing processes of several temporal domains and point out the similarities between brain correlates of timing and ADHD brain pathology. Furthermore, we review and provide new direct fMRI evidence that ADHD children show dysfunctions in timing–mediating prefrontal, cingulate, striatal and cerebellar brain regions during cognitive time management across several temporal domains such as time discrimination of milliseconds, motor timing to seconds and temporal discounting of longer intervals of weeks to years. Given that impulsiveness, timing deficits and more specifically ADHD have been related to dopamine dysregulation, we tested the effect of the dopamine agonist MPH on brain dysfunction during a time-discrimination task. Despite no significant performance effects, MPH normalized all brain dysfunctions in ADHD patients. The findings show the superior sensitivity of the brain compared with behaviour to medication effects in ADHD and reinforce the importance of the role of dopamine-mediated timing dysfunctions in the impulsive pathology of ADHD. Future studies should investigate whether other pharmacological agents such as the noradrenaline agonist atomoxetine or behavioural interventions can normalize timing-related brain dysfunction in ADHD. We believe that the role of a disruption of temporal processes underlying the impulsive pathology of ADHD is relatively under-investigated and hope this review motivates more research into the timing aspects of ADHD.

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