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Review

Meta-analysis of fMRI studies of timing in attention-deficit hyperactivity disorder (ADHD)

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ABSTRACT

Attention-deficit hyperactivity disorder (ADHD) is associated with deficits in timing functions with, however, inconclusive findings on the underlying neurofunctional deficits. We therefore conducted a meta-analysis of 11 functional magnetic resonance imaging (fMRI) studies of timing in ADHD, comprising 150 patients and 145 healthy controls. Peak coordinates were extracted from significant case–control activation differences as well as demographic, clinical, and methodological variables. In addition, meta-regression analyses were used to explore medication effects.

The most consistent deficits in ADHD patients relative to controls were reduced activation in typical areas of timing such as left inferior prefrontal cortex (IFC)/insula, cerebellum, and left inferior parietal lobe. The findings of left fronto-parieto-cerebellar deficits during timing functions contrast with well documented right fronto-striatal dysfunctions for inhibitory and attention functions, suggesting cognitive domain-specific neurofunctional deficits in ADHD. The meta-regression analysis showed that right dorsolateral prefrontal cortex (DLPFC) activation was reduced in medication-naïve patients but normal in long-term stimulant medicated patients relative to controls, suggesting potential normalization effects on the function of this prefrontal region with long-term psychostimulant treatment.

Contents

1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is defined in the DSM-IV-TR by age-inappropriate impulsiveness, inattention and hyperactivity (Achenbach, 1994) and is one of the most debilitating childhood disorders, persisting into adulthood in about 65% of cases (Faraone and Biederman, 2005). While cognitive deficits in executive functions are relatively well established (Rubia, 2011; Willcutt et al., 2005), ADHD patients have also consistent deficits in timing functions (Noreika et al., in press; Rubia et al., 2009a; Toplak et al., 2006). Timing functions are closely associated with impulsiveness, typically defined as a premature (i.e., badly timed), impatient and delay averse (i.e., the passage of time seems subjectively more intolerable) response pattern that does not consider consequences of

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one's acts (i.e., poor temporal foresight) (Rubia et al., 2009a). In fact, ADHD children have shown to have deficits in motor timing, time estimation and temporal foresight (Noreika et al., in press; Rubia et al., 2009a; Toplak et al., 2006). Despite consistent evidence for timing deficits, however, relatively few functional magnetic resonance imaging studies have measured the neurofunctional substrates of these functions, with inconsistent findings.

Five functional magnetic resonance imaging (fMRI) studies have compared ADHD patients with controls during motor timing. An early study from our lab found relatively small differences between 7 ADHD patients and 9 healthy boys during a sensorimotor synchronization task of 600 ms in occipital brain regions (Rubia et al., 2001). During freely timed finger sequencing ADHD children relative to controls had reduced parietal activation (Mostofsky et al., 2006). In ADHD adults, timed and untimed sensorimotor synchronization was associated with decreased activation in typical areas of sub-second sensorimotor synchronization including inferior and orbitofrontal cortex, premotor cortex, basal ganglia, insula, parietal lobes and cerebellum (Valera et al., 2010). Two studies using delay tasks of second intervals measuring suprasecond sensorimotor anticipation showed reduced activation in ADHD children in key areas of sensorimotor anticipation (Wiener et al., 2010a) in anterior and posterior cingulate and pre-SMA (Rubia et al., 1999) as well as dorsolateral prefrontal cortex, striato-thalamic and parietal regions (Christakou et al., in press). One of these studies, however, also observed enhanced activation in a more posterior part of the SMA (Rubia et al., 1999). A study measuring the brain response to unpredictable relative to predictable stimuli found reduced cerebellar activation in ADHD children relative to controls, however, in only one of two samples (Durston et al., 2007). Three fMRI studies tested for the neural substrates of time discrimination of hundreds of milliseconds in adolescents with ADHD in the same or similar paradigms, and found reduced activation in right dorsolateral prefrontal cortex and anterior cingulate/supplementary motor area (Smith et al., 2008), in orbitofrontal, inferior and medial frontal areas, including anterior cingulate, and in caudate and cerebellum (Rubia et al., 2009a) and in rostral anterior cingulate and cerebellum (Vloet et al., 2010). Only two studies measured temporal foresight in temporal discounting paradigms in ADHD patients. In our whole-brain analysis, ADHD patients showed reduced activation relative to controls during the delayed choices in regions that have previously been associated with temporal foresight (Christakou et al., 2011; Wittmann et al., 2007), such as bilateral inferior prefrontal cortex, insula, basal ganglia, parietal regions and the cerebellum (Rubia et al., 2009a). The second study used a region of interest approach and showed reduced activation in the ventral striatum for immediate reward choices but enhanced activation in the dorsal striatum and amygdala for delayed reward choices, presumably tapping into temporal foresight and/or limbic mechanisms mediating delay aversion (Plichta et al., 2009).

In conclusion, the functional brain imaging findings confirm the notion that ADHD patients have difficulties in the recruitment of the key areas that mediate temporal processes (Wiener et al., 2010a, 2010b). While studies have used a variety of timing tasks, a recent meta-analysis of timing functions in healthy adults showed that there is a relatively large overlap in brain areas that mediate these different subsecond and suprasecond motor and perceptual timing functions, suggesting that there are neural networks that mediate timing functions across temporal domains and sensory modalities (Wiener et al., 2010a). These key timing areas include the inferior and dorsolateral prefrontal cortex, the cerebellum and parietal lobes (Rubia, 2006; Rubia and Smith, 2004; Wiener et al., 2010a, 2010b). Lateral prefrontal regions, including the insula, are thought to be a temporal accumulator underlying motor and perceptual timing functions; the cerebellum is considered a key region for temporal prediction; while parietal regions are thought to be crucial for implicit timing and attention to temporal information (Rubia, 2006; Rubia and Smith, 2004; Wiener et al., 2010a, 2010b). The basal ganglia are also involved as a hypothesized "internal clock", presumably by integrating cortical oscillating activity, but are more prominently active during subsecond timing functions (Coull et al., 2011; Rubia, 2006; Rubia and Smith, 2004; Wiener et al., 2010a). Thus, ADHD patients appear to show brain function abnormalities during timing functions in these key timing areas, including inferior and dorsolateral prefrontal regions (Christakou et al., in press; Rubia et al., 1999, 2009a; Smith et al., 2008; Valera et al., 2010; Vloet et al., 2010), the cerebellum (Durston et al., 2007; Rubia et al., 2009a; Valera et al., 2010; Vloet et al., 2010), the basal ganglia (Christakou et al., in press; Plichta et al., 2009; Rubia et al., 2009a; Valera et al., 2010; Vloet et al., 2010) and the parietal lobes (Christakou et al., in press; Mostofsky et al., 2006; Rubia et al., 2009a; Valera et al., 2010) (Table 1).

However, findings have not always been consistent. With a few exceptions (Rubia et al., 2009a; Smith et al., 2008), the majority of studies were conducted in previously medicated patients, which, given the strong positive association between dopamine agonists and timing processes (Coull et al., 2011; Rubia, 2006) suggest that deficit findings may be overshadowed by long-term stimulant effects on brain function (Rubia, 2006). This is further reinforced by our findings that a single dose of MPH normalized all fronto-striato-cerebellar deficits observed during time discrimination under placebo (Rubia et al., 2009a). Potential normalization of brain deficits with stimulant medication is further reinforced by meta-regression analyses in structural and biochemical imaging data which showed that long-term stimulant medication is associated with more normal basal ganglia volumes (Nakao et al., 2011) and an upregulation of striatal dopamine transporter levels (Fusar-Poli et al., 2012). Also, comorbidity with antisocial behaviors such as conduct disorder is rarely controlled for in imaging studies, but is likely to impact upon the deficit findings (Rubia, 2011).

In this meta-analysis, we thus aimed to establish the most consistent functional imaging differences between ADHD patients and controls during functions of timing, addressing potential confounds of long-term stimulant medication and comorbidity. For this purpose, we included all whole-brain analysis fMRI studies that used timing paradigms, and, in addition, tested for effects of stimulant medication history as well as comorbidity in meta-regression analyses.

We hypothesized that ADHD patients would show consistent brain dysfunctions in key regions involved in timing functions in healthy populations, including the cerebellum, inferior prefrontal cortex, basal ganglia and inferior parietal lobe. Furthermore, we hypothesized that stimulant medication would be associated with attenuated deficits in these brain regions.

2. Methods

A comprehensive literature search of whole-brain fMRI studies conducting comparisons between patients with ADHD and healthy controls using tasks of timing functions was conducted using the PubMed, ScienceDirect, Google Scholar, Web of Knowledge and Scopus search engines. The search keywords were "Attention-deficit hyperactivity disorder"; "ADHD" or "hyperkinetic"; plus "fMRI"; plus "time"; "timing"; "temporal"; "delay"; "synchronized" or "finger-tapping". In addition; manual searches were conducted within review papers and reference sections of individual papers. We excluded studies that (1) contained subject overlap within the same task with other studies (2) used a region-of-interest (ROI) approach and (3) did not report co-ordinates for the relevant contrasts and did/could not supply these when contacted. The corresponding authors were asked to provide additional details

Table 1
Characteristics and results of the 11 fMRI datasets included in the meta-analysis.

Authors	Task	Modality	Time interval	Design	*N*	ADHD patients				Healthy controls			Brain regions	
						Mean age (SD)	% Male	% Medicated (time stopped)	Co-morbid (%)	*N*	Mean age (SD)	% Male	Controls > ADHD	ADHD > Controls
Rubia et al. (2001)	Synchronized finger tapping	Visual	600 ms	B	7	15.71 (2.1)	100	57.1 (7 days)	3 CD (42.86)	9	15.01 (2.3)	100	R lateral visual cortex	R medial visual cortex
Valera et al. (2010)	Synchronised finger sequencing	Auditory	500 ms	B	21	34 (10.1)	71	67 lifetime: 5 not current; 9 current (24 h)	0	19	32.7 (10.6)	63	L IFC/OFC B insula, B PreCG B inf PL L MTC/STC R Cb	/
Valera et al. (2010)	Unsynchronised finger sequencing	Auditory	500 ms	B	21	34 (10.1)	71	67 lifetime: 5 not currently; 9 current (24 h)	0	19	32.7 (10.6)	63	B IFC R OFC R amygdala, L PreCG L cau-date/putamen L insula, L amygdala, B Cb	/
Mostofsky et al. (2006)	Sequential finger tapping	Visual	~500 ms	B	11	10.4 (1.2)	73	73 (2 days)	1 0DD (9)	11	10.4 (1.4)	73	R inferior PL R superior PL	/
Rubia et al. (1999)	Delay Task	Visual	5 s	B	7	15.71 (2.1)	100	57.1 (7 days)	3 CD (42.86)	9	15.01 (2.3)	100	R MFC/ACC PCC	SMA
Christakou et al. (in press)	Delay/Vigilance Task	Visual	2 s, 5 s, 8 s	ER	20	14 (1.7)	100	40 (36 h)	0	20	14.7 (2.2)	100	L DLPFC thalamus putamen hippocampus LPre/PostCG/Sup PL	M PREC/cuneus
Durston et al. (2007), sample 1	Expectancy violation	Visual	2 s	B	10	11.6 (2.6)	80	50 (24 h)	4 ODD (40)	10	11.9 (2.1)	80	/	/
Durston et al. (2007), sample 2	Expectancy violation	Visual	2 s	B	10	14.9 (2.3)	100	70 (24 h)	4 ODD(40)	9	15.0 (2.1)	100	L inferior Cb	/
Rubia et al. (2009a)	Time discrimination	Visual	300–500 ms difference	B	12	13 (1)	100	0	1 CD (8.3)	12	13 (1)	100	B OFC/IFC/MFC/ACC B caudate, R Cb	/
Smith et al. (2008)	Time discrimination	Visual	300–500 ms difference	B	21	12.8 (1.6)	100	0	3 CD/ODD (14.29)	17	14.0 (2.1)	100	R DLPFC ACC/SMA	/
Rubia et al. (2009a)	Temporal discounting	Visual	Week, month, year	B	10	14 (2)	100	60 (36 h)	1 CD (10)	10	15 (4)	100	B IFC/L OFC L thalamus, putamen, L inf PL, L PREC/PCC L Cb, brainstem	/

Abbreviations: B: block; ER: event-related; CD: conduct disorder; ODD: oppositional defiant disorder; IA: inattentive subtype; HI: hyperactive-impulsive subtype; C: combined subtype; NOS: not otherwise specified subtype; B: bilateral; L: left; R: right; BA: Brodmann's area; ACC: anterior cingulate cortex; Cb: cerebellum; DLPFC: dorsolateral prefrontal cortex; IFC: inferior frontal cortex; MFC: middle frontal cortex; OFC: orbitofrontal cortex; PCC: posterior cingulate cortex; PreCG: precentral gyrus; PostCG: postcentral gyrus; PREC: precuneus; SFG: superior frontal gyrus; SMA: supplementary motor area; PL: parietal lobe; STC: superior temporal cortex; MTC: medial temporal cortex.

not included in the original publications. MOOSE guidelines for meta-analyses of observational studies were followed in the study (Stroup et al., 2000).

A meta-analysis was carried out which included studies on the following timing tasks: auditory or visual tasks of motor timing such as free, sequential or synchronized finger tapping (where subjects had to either tap one finger on a button box (finger tapping) or tap their fingers sequentially against their thumb (sequential finger tapping) in a freely chosen rhythm, or had to synchronize their finger tapping with a predetermined temporal rhythm (synchronized finger tapping), all of these within several hundreds of milliseconds), temporal synchronization in visual motor delay tasks (where participants had to make a motor response in synchrony to a visual stimulus that appeared in fixed intervals of several seconds); time estimation tasks (where participants had to discriminate between temporal intervals that differed by several hundreds of milliseconds); tasks that manipulate temporal prediction (i.e., the temporal expectancy of a visual stimulus that had to be responded to was modulated, being either predictable or unpredictable and the task measures the brain response to unpredictable versus predictable delays, thus measuring temporal prediction); and tasks of temporal foresight (i.e., measured in temporal discounting tasks, where participants have to choose between an immediate, smaller and a larger, but delayed reward; the task measures to what degree a reward is being discounted in proportion of its delay, tapping into individual sensitivity to the passage of time, temporal foresight and inter-temporal decision making).

Peak coordinates of activation differences between ADHD patients and controls were extracted from each dataset for the timing function versus their respective control contrasts. Importantly, those peaks which did not appear statistically significant at the whole-brain level were excluded.

Regional differences in activation during timing tasks between patients and controls were analyzed using Effect-Size Signed Differential Mapping (ES-SDM) software (http://www.sdmproject.com), a voxel-based meta-analytic approach which uses the reported peak coordinates to recreate maps of the effect size of the differences in BOLD response between patients and controls. In the case of peak coordinates, the recreation is based on first converting the peak t-value to Hedge's effect size and then applying an un-normalized Gaussian kernel to the voxels close to the peak. The SDM methods have been described in detail elsewhere (Radua and Mataix-Cols, 2009, 2010; Radua et al., 2011) and only the main points are summarized here.

First, to ensure that brain regions in which researchers are more liberal, do not falsely appear as more consistent in the meta-analyses, only datasets in which the same threshold is used throughout the whole brain are included. Second, activations and deactivations are recreated in the same map in order to correctly analyze those regions with higher between-study heterogeneity (i.e., where randomly some studies report activation and some deactivation). If activations and deactivations were plotted in separate maps, noisy regions could falsely appear as activating and deactivating at the same time – which is logically impossible (Radua and Mataix-Cols, 2010). Third, studies are combined with a random-effects model as in standard meta-analyses, thus taking into account sample-size, intra-study variability and between-study heterogeneity (Radua et al., in press).

These analyses were complemented with analyses of robustness. In case of significant heterogeneity, within a brain region found to abnormally respond in patients, we used funnel plots to check whether findings might have been driven by few or small studies, as well as to detect gross abnormalities such as studies reporting opposite results (Radua and Mataix-Cols, 2010; Radua et al., 2011). Also, we conducted a jackknife sensitivity analysis consisting of iteratively repeating the same analysis excluding one dataset at a time in order to establish whether the results were replicable (Radua and Mataix-Cols, 2009).

Statistical significance was determined using standard permutation tests, creating null distributions from which p-values could be directly obtained. Default ES-SDM thresholds were used (voxel $p = 0.005$, peak height $Z = 1$, cluster extent = 10 voxels) (Radua and Mataix-Cols, 2010). We conducted a meta-regression analysis for the percentage of patients receiving long-term stimulant medication and percentage of patients with co-morbid psychiatric diagnoses. While the main meta-analysis is a direct combination of the results of the included studies, meta-regression analyses involve additional degrees of inference, which might distort the expected false positive rate. Therefore, as in previous meta-analyses (Radua and Mataix-Cols, 2009; Via et al., 2011), we used a 10-times lower threshold (i.e., $p < 0.0005$) in order to minimize the probability of false positives or the detection of spurious relationships. In addition we required for abnormalities to be detected both in the slope and in one of the extremes of the regressor (e.g., in studies where 0% or where 100% of the patients were receiving medication) (Radua and Mataix-Cols, 2009; Via et al., 2011). A meta-regression with age could not be carried out due to lack of variation of age, as only 2 of the 11 datasets were adult.

3. Results

3.1. Included studies and characteristics

The search retrieved a total of 13 datasets for timing tasks. Two studies were excluded due to use of anatomical ROIs (Plichta et al., 2009; Vloet et al., 2010). Finally, 11 high-quality datasets were included in the meta-analysis, 2 adult (Valera et al., 2010) and 9 pediatric studies (Christakou et al., in press; Durston et al., 2007; Mostofsky et al., 2006; Rubia et al., 1999, 2001, 2009a; Smith et al., 2008). Some of the included papers contained more than one independent dataset (Table 1). These 11 timing datasets included in total 150 ADHD patients and 145 healthy controls (Table 1).

3.2. Meta-analysis results

At the specified threshold of $p < 0.005$, compared to controls, ADHD patients showed significantly decreased activation in the vermis of the cerebellum, in a cluster comprising left inferior prefrontal cortex and insula, and in left supramarginal gyrus extending into left superior temporal and post central gyri (Table 2 and Fig. 1). ADHD patients, relative to controls, also showed significantly increased activation in bilateral precuneus extending to cuneus and posterior cingulate cortex (Table 2 and Fig. 1). Additionally, at a more lenient threshold of $p < 0.05$, ADHD patients showed decreased activation of right dorsolateral prefrontal cortex (DLPFC) compared to controls (Table 2 and Fig. 1).

3.3. Reliability analyses

A whole-brain jackknife sensitivity analysis showed that the findings in the right cerebellum, left supramarginal gyrus and bilateral precuneus/posterior cingulate were highly replicable, preserved throughout all of the 11 combinations of datasets. The left inferior prefrontal cortex (IFC)/insula result remained significant in all but 2 combinations of datasets (Table 3).

3.4. Effect of long-term stimulant medication

Information on stimulant medication was available for all 11 datasets, with 70 patients (47%) receiving stimulant medication at study time (methylphenidate, $N = 39$, unidentified stimulants, $N = 28$, D-amphetamine, $N = 3$). At $p < 0.0005$, the meta-regression

Table 2
Results of meta-analyses for fMRI timing tasks: regional differences in activation between individuals with ADHD and healthy controls for timing tasks at $p < 0.005$, $z > 1$ and cluster size > 10 voxels.

Contrasts	Talairach coordinates	SDM *z*-value	*p*-value	No. of voxels	Breakdown (no. of voxels)
Controls > ADHD					
R cerebellum vermis	16, −46, −22	−2.143	0.0003	403	R vermis (403)
L inferior frontal cortex/insula	−34, 16, 12	−1.931	0.001	76	L BA 12 (23) L BA 44 (21) L BA 45 (17) L BA 22 (12)
L supramarginal gyrus/superior temporal/postcentral gyri	−52, −48, 30	−2.051	0.0006	137	L BA 40 (90) L BA 12 (12) L BA 2/3/40 (14) L BA 22/40/41 (11)
* R dorsolateral prefrontal cortex	42; 42; 6	−1.470	0.017	95	R BA 10 (75) R BA 46 (11)
ADHD > Controls					
B precuneus/cuneus/posterior cingulate	6, −64, 26	1.427	0.000002	818	B BA 7 (346) B BA 31 (269) B BA 18 (121) B BA 23 (53) R BA 19 (29)
Effect of stimulant medication history					
Unmedicated patients < long-term medicated patients and controls					
R dorsolateral prefrontal cortex	34, 50, 6	3.208	0.00007	47	R BA 10 (47)
Effect of comorbidity (none)					

Peak, statistics and cluster breakdown refer to the comparison between both groups of patients. Meta-regressions for effects of medication and comorbidity are reported at $p < 0.0005$. *Abbreviations*: No: number, R: right, L: left, P: *p*-value, SDM: signed differential mapping, BA: Brodmann's area.
* Differences between patients and controls at a more lenient level of $p < 0.05$.

analysis with long-term stimulant medication showed that the percentage of patients on long-term stimulant medication correlated significantly with increasing activation in right DLPFC, so that medication-naïve patients had significantly reduced activation in right DLPFC compared to both healthy controls and long-term medicated patients, who did in turn not differ from each other (Table 2 and Fig. 2).

3.5. Effect of comorbidity

Information on co-morbidity was available for all 11 datasets, with 20 patients (13%) having co-morbid psychiatric conditions (CD $N = 10$, ODD $N = 10$). The meta-regression with percentage of patients with comorbidities as a regressor revealed no significant results at the pre-established statistical threshold.

4. Discussion

This meta-analysis of fMRI studies of timing functions in ADHD shows consistent and replicable deficits in patients relative to controls in key areas that are known to mediate timing functions in healthy individuals, including the cerebellum, left inferior prefrontal cortex and left inferior parietal lobes. ADHD patients, on the other hand, showed consistently enhanced activation relative to controls in precuneus and posterior cingulate, presumably reflecting problems with deactivation of the default mode network

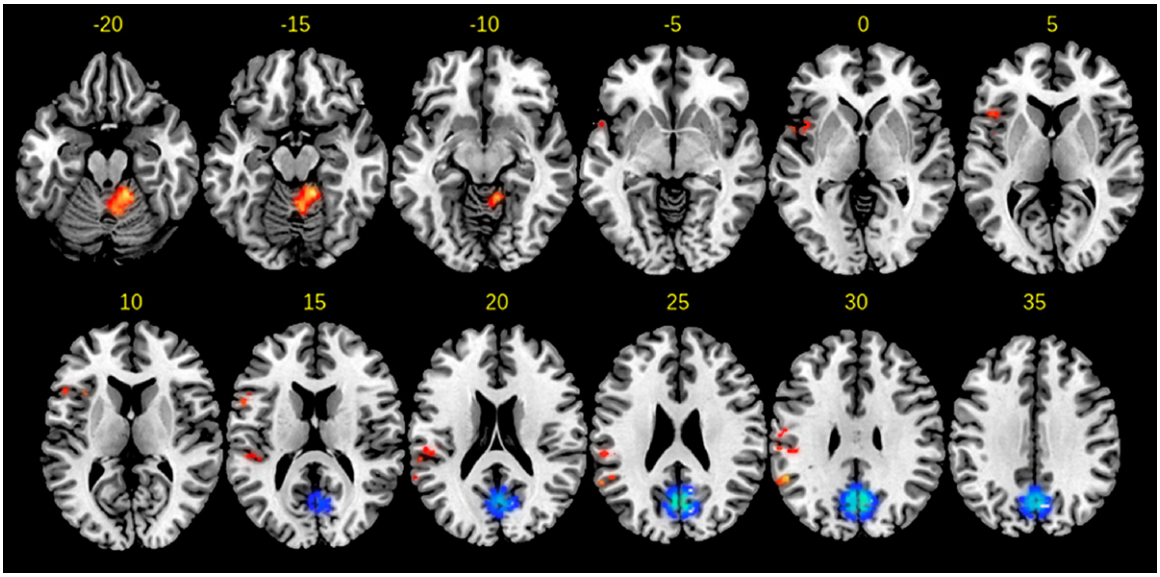

Fig. 1. Regions of decreased (red/orange) and increased (blue) activation in individuals with ADHD compared with healthy controls for timing tasks ($p < 0.005$). Decreased activation in ADHD patients relative to controls is shown in right cerebellum, left supramarginal gyrus and left IFC/insula. Increased activation in ADHD relative to controls was in bilateral precuneus and posterior cingulate.

Table 3
Results of the jackknife reliability analyses.

Dataset	R cerebellum 16, −46, −22	L parietal −52, −48, 30	L IFG/insula −34, 16, 12	Precuneus 6, −64, 26
Rubia et al. (2001)	Yes	Yes	Yes	Yes
Valera et al. (2010) (synchronized)	Yes	Yes	No	Yes
Valera et al. (2010) (free)	Yes	Yes	No	Yes
Mostofsky et al. (2006)	Yes	Yes	Yes	Yes
Rubia et al. (1999)	Yes	Yes	Yes	Yes
Christakou et al. (in press)	Yes	Yes	Yes	Yes
Durston et al. (2007) (sample 1)	Yes	Yes	Yes	Yes
Durston et al. (2007) (sample 2)	Yes	Yes	Yes	Yes
Rubia et al. (2009a) (discrimination)	Yes	Yes	Yes	Yes
Smith et al. (2008)	Yes	Yes	Yes	Yes
Rubia et al. (2009a) (discounting)	Yes	Yes	Yes	Yes
Total	11 out of 11	11 out of 11	9 out of 11	11 out of 11

Yes: brain region remains significantly increased/decreased in the jackknife analysis when the dataset in question is excluded. No: brain region is no longer significantly increased/decreased in those analyses.

(DMN). Furthermore, the meta-regression analysis provided evidence that long-term stimulant medication may be associated with more normal function in right DLPFC. This region was only underactivated in medication-naïve patients, and in the entire sample at a more lenient threshold, while it was normal in long-term medicated patients. This suggests that the inclusion of previously medicated patients overshadowed right frontal brain function deficits in ADHD patients, which may be "normalized" with medication. The meta-regression analysis for comorbidity, on the other hand, showed no effects, suggesting that functional deficits in frontal, cerebellar and parietal regions during timing functions are associated with ADHD and not with comorbid pathophysiology.

ADHD patients showed consistently reduced activation across all fMRI studies of timing in a predominantly left-hemispheric network of left inferior prefrontal cortex and insula, inferior parietal cortex and cerebellum. These regions have consistently been associated with timing functions (Coull et al., 2011; Rubia, 2006; Rubia and Smith, 2004; Wiener et al., 2010a, 2010b). Inferior prefrontal cortex and insula have been associated with subsecond as well as suprasecond motor and perceptual timing functions as well as temporal foresight and are thought to represent a temporal accumulator. Left-hemispheric IFG and insula in particular are thought to play a role in beat-based and counting strategies for timing functions (Wiener et al., 2010a) but have also been shown to mediate temporal foresight (Christakou et al., 2011; Wittmann et al., 2007). The role of the cerebellum for timing functions is well established, most prominently mediating temporal predictions (Coull et al., 2011), which are important for both motor and perceptual timing tasks (Wiener et al., 2010a) as well as for the prediction of temporal consequences of behavior in temporal discounting tasks (Christakou et al., 2011). The medial cerebellum in particular is important for visual timing functions (Coull et al., 2011), which was the predominant modality in this meta-analysis (with only 2 studies using the auditory modality). The left inferior parietal lobe has been shown to be crucial for temporal prediction (Coull et al., 2011; Wiener et al., 2010b) as well as for attention to time (Rubia, 2006; Rubia and Smith, 2004; Wiener et al., 2010a). Interestingly, we did not observe basal ganglia deficits. This may be due to the fact that the basal ganglia are most prominently implicated in subsecond timing mechanisms, while we included several suprasecond timing tasks. In conclusion, this meta-analysis shows that ADHD patients have problems with the recruitment of key regions that form part of a neural network that is responsible for timing functions across several temporal and sensory domains.

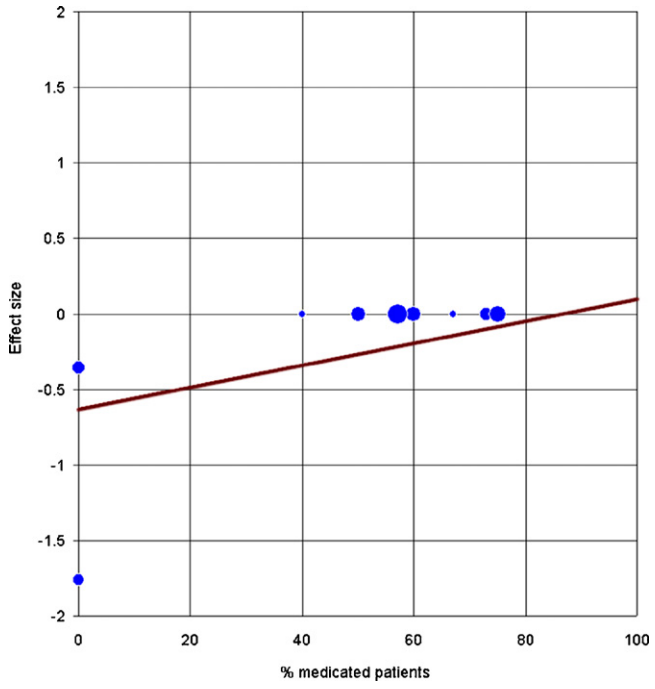

Fig. 2. Meta-regression analysis for timing tasks shows that the percentage of patients receiving long-term psychostimulant treatment is associated with more normal right dorsolateral prefrontal activation relative to healthy controls. The regression line (meta-regression signed differential mapping slope) is presented as a straight line.

The left hemispheric laterality of the fronto-parietal activation deficits contrasts with the laterality findings of previous meta-analyses that showed predominantly right hemispheric fronto-striato-thalamic deficits in ADHD patients during tasks of cognitive control (Dickstein et al., 2006; Hart et al., in press) and right hemispheric fronto-parietal underactivation during tasks of attention (Hart et al., in press). Recent reviews also confirm more predominantly right rather than left IFG dysfunction in ADHD children and adults during tasks of cognitive and inhibitory control (Cubillo et al., 2012; Durston et al., 2011; Rubia, 2011). While inhibitory control is mediated by right IFG (Chambers et al., 2009; Rubia et al., 2003), and attention functions are mediated by predominantly right hemispheric fronto-parietal networks (Kanwisher and Wojciulik, 2000; Cabeza and Nyberg, 2000), timing functions, in particular time perception, are mediated by bilateral but predominantly left hemispheric regions (Wiener et al., 2010a, 2010b). The findings therefore suggest that ADHD patients have domain-specific deficits in task-relevant frontal lobe regions and their corresponding fronto-striatal, fronto-parietal and fronto-cerebellar networks, rather than a right-lateralized frontal brain dysfunction, as has previously been suggested (Dickstein et al., 2006). Domain-specific deficits in different task-dependent fronto-striatal inhibitory and fronto-cerebellar timing networks in ADHD

are also indicated in this meta-analysis by the deficits in the cerebellum, which is a key region mediating timing functions together with prefrontal areas (Coull et al., 2011; Rubia, 2006; Rubia and Smith, 2004; Wiener et al., 2010a). Cerebellar deficits have most prominently been observed in ADHD patients during timing functions (Durston et al., 2007; Rubia et al., 2009a; Valera et al., 2010; Vloet et al., 2010) (Table 1) and are not typically observed in the context of cognitive control. This meta-analysis of timing thus shows deficits in a predominantly left-hemispheric fronto-parieto-cerebellar neural network of timing functions that is different from the right-hemispheric fronto-striatal or fronto-parietal deficits that are typically observed in the context of inhibitory control or attention, suggesting that ADHD patients have cognitive domain-dependent neuro-functional deficits in different neural networks depending on the cognitive context.

The functional deficit findings in these regions parallel structural imaging findings that show that the vermis of the cerebellum is one of the most consistent areas of structural abnormality, followed by inferior prefrontal brain regions (Shaw et al., 2009; Valera et al., 2007). Both frontal and parietal brain regions, furthermore, have been shown to be delayed in the peak of cortical thickness and surface area in ADHD patients in longitudinal structural imaging studies, thought to reflect late cognitive maturation (Shaw et al., 2007, 2012). Interestingly, developmental functional imaging studies of timing functions show that the same left inferior frontal and cerebellar activations that were reduced in ADHD patients relative to their age-matched peers in this meta-analysis, are progressively age-correlated between childhood and adulthood, suggesting a potential delay also in functional brain maturation in ADHD patients (Christakou et al., 2011; Smith et al., 2011).

Long-term stimulant medication significantly attenuated right DLPFC activation dysfunction which was only observed in medication-naïve patients, and in the entire sample only at a more lenient threshold (Table 2). Two previous meta-analyses in ADHD patients showed that stimulant medication is associated with more normal basal ganglia volumes (Nakao et al., 2011) as well as with increased striatal dopamine transporter levels (Fusar-Poli et al., 2012). Other structural imaging studies have shown more normal inferior prefrontal cortical thickness development in long-term medicated relative to medication-naïve ADHD patients (Shaw et al., 2009). Functional MRI studies have shown that single as well as chronic doses of MPH can upregulate and even normalize frontal and striatal brain activation in ADHD patients during time discrimination (Rubia et al., 2009a) and other cognitive functions (Bush et al., 2008; Rubia et al., 2009b, 2011a, 2011b). Our meta-analytic findings of more normal DLPFC activation in long-term medicated ADHD patients are therefore in line with and extend previous evidence that MPH is associated with more normal frontal and striatal brain structure and function. Nevertheless, the findings need to be interpreted with caution as they were driven by the two medication-naïve samples included in the study (Rubia et al., 2009a; Smith et al., 2008). Furthermore, while in the studies from our group, non-responders were not included (i.e., Rubia et al., 2001, 1999, 2009a, 2009b; Christakou et al., in press; Smith et al., 2008), no information on the inclusion of non-responders was provided in the other 5 studies. Also, hardly any information on symptom severity was provided for most papers. We therefore cannot exclude the possibility that differences between studies in ADHD symptom severity or that the inclusion of non-responders in some of the studies may have confounded the meta-regression findings.

Comorbidity, on the other hand, had no effect on the neuro-functional timing deficit findings. This suggests that comorbidity with conduct disorder and/or oppositional defiant disorder, which was the predominant comorbidity in all studies, is not associated with the brain dysfunctions, which thus appear inherent to ADHD pathophysiology. However, given that there was only a small proportion of comorbid patients (13%), the findings need to be considered preliminary.

ADHD patients relative to controls had enhanced activation in precuneus and posterior cingulate gyrus. These areas have not been specifically associated with timing functions, but are key areas of visual-spatial attention (Mesulam et al., 2001) and may thus have mediated visual-spatial attention to temporal information to compensate for reduced lateral fronto-parietal activation. This interpretation of an attention role for this activation would be in line with fMRI studies that found these areas to be enhanced in ADHD children and adults relative to controls during visual-spatial attention tasks (Cubillo et al., 2012; Rubia et al., 2009b). An alternative, perhaps more plausible hypothesis, is that the enhanced precuneus/posterior cingulate activation in ADHD reflects problems with deactivating the DMN of self-referential thoughts, that is typically switched off during cognitively demanding tasks in healthy subjects (Weissman et al., 2006), and which in turn is associated with optimal task performance and fewer attention lapses in healthy and ADHD subjects (Broyd et al., 2009; Weissman et al., 2006). This interpretation would be in line with previous records of abnormal DMN activity in ADHD, which has been associated with poor cognitive performance (Broyd et al., 2009; Christakou et al., in press).

This study has several limitations, some inherent to all meta-analyses. First, peak-based meta-analyses are based on coordinates from published studies rather than raw statistical brain maps, which may provide less accurate results (Radua et al., in press). Studies with low statistical power may have failed to detect and report a true case–control difference. ES-SDM would have imputed these effect-sizes as zero when in fact these may not have been zero. This would have caused the estimated effect-size to be downwards-biased and the heterogeneity to be enlarged, ultimately resulting in a low *z*-value. In such cases, the *z*-value obtained in this meta-analysis would have been higher if we had included the raw statistical parametric maps rather than significant peak-based analyses. While this meta-analysis may therefore have failed to detect true effects in regions where effect-sizes were not significant in the included studies, it should be outlined, however, that these true effects would also have been the weakest, as otherwise they would have been detected in some of the included studies.

Second, the different studies included in this meta-analysis used different statistical thresholds. However, while thresholds involving correction for multiple comparisons are usually preferred, the inclusion of studies with more liberal thresholds is still statistically correct. Indeed, SDM preprocessing uses the coordinates of the voxels with the greatest differences to approximately recreate the statistical parametric map, but does not make assumptions about whether or not these differences were significant (Radua et al., in press). Third, while voxel-wise meta-analytical methods provide excellent control for false positive results, it is more difficult to avoid false negative results (Radua et al., in press).

Given that the fMRI literature of timing functions is relatively small, we combined tasks that cover a range of different timing functions, such as motor timing, time perception and temporal discounting. It could be argued that future meta-analytic studies, once a wider range of fMRI studies of timing functions is available, should further subdivide analyses according to subdomains of temporal functions. However, a recent meta-analysis of timing functions in healthy adults revealed a surprising overlap in brain areas that mediate subsecond and suprasecond timing, as well as motor and perceptual timing functions, suggesting that there are cross-modal and cross-temporal fronto-parieto-cerebellar neural networks of timing (Wiener et al., 2010a).

In conclusion, this meta-analysis shows consistent deficits in ADHD patients in typical brain regions that are associated with

timing functions, including left inferior prefrontal, parietal and cerebellar regions. The left lateralized fronto-parieto-cerebellar dysfunction findings contrast with typical right lateralized fronto-striatal and fronto-parietal deficits during inhibition and attention tasks (Hart et al., in press), suggesting cognitive domain-specific neurofunctional deficits. Furthermore, long-term stimulant medication appears to be associated with normal right dorsolateral prefrontal activation, which was only dysfunctional in medication-naïve patients.

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References

Achenbach, T.M., 1994. Manual for the Child Behaviour Checklist/4–18 and 1991 Profile. University of Vermont, Burlington, VT.

Broyd, S.J., Demanuele, C., Debener, S., Helps, S.K., James, C.J., Sonuga-Barke, E.J.S., 2009. Default-mode brain dysfunction in mental disorders: a systematic review. Neuroscience and Biobehavioral Reviews 33, 279–296.

Bush, G., Spencer, T.J., Holmes, J., Shin, L.M., Valera, E.M., Seidman, L.J., Makris, N., Surman, C., Aleardi, M., Mick, E., Biederman, J., 2008. Functional magnetic resonance imaging of methylphenidate and placebo in attention-deficit/hyperactivity disorder during the multi-source interference task. Archives of General Psychiatry 65, 102–114.

Cabeza, R., Nyberg, L., 2000. Imaging cognition II: an empirical review of 275 PET and fMRI studies. Journal of Cognitive Neuroscience 12, 1–47.

Chambers, C.D., Garavan, H., Bellgrove, M.A., 2009. Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. Neuroscience and Biobehavioral Reviews 33, 631–646.

Christakou, A., Brammer, M., Rubia, K., 2011. Maturation of limbic corticostriatal activation and connectivity associated with developmental changes in temporal discounting. NeuroImage 54, 1344–1354.

Christakou, A., Murphy, C., Chantiluke, C., Cubillo, A., Smith, A., Giampietro, V., Daly, E., Ecker, C., Robertson, D., Murphy, C., Rubia, K. Disorder-specific functional abnormalities during sustained attention in youth with attention deficit hyperactivity disorder (ADHD) and with autism. Molecular Psychiatry, http://dx.doi.org/10.1038/mp.2011.185, in press.

Coull, J.T., Cheng, R.-K., Meck, W.H., 2011. Neuroanatomical and neurochemical substrates of timing. Neuropsychopharmacology 36, 3–25.

Cubillo, A., Halari, R., Smith, A., Taylor, E., Rubia, K., 2012. Fronto-cortical and fronto-subcortical brain abnormalities in children and adults with ADHD: a review and evidence for fronto-striatal dysfunctions in adults with ADHD followed up from childhood during motivation and attention. Cortex 48, 194–215.

Dickstein, S.G., Bannon, K., Castellanos, F.X., Milham, M.P., 2006. The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis. Journal of Child Psychology and Psychiatry 47, 1051–1062.

Durston, S., Davidson, M.C., Mulder, M.J., Spicer, J.A., Galvan, A., Tottenham, N., Scheres, A., Castellanos, F.X., van Engeland, H., Casey, B.J., 2007. Neural and behavioral correlates of expectancy violations in attention-deficit hyperactivity disorder. Journal of Child Psychology and Psychiatry 48, 881–889.

Durston, S., van Belle, J., de Zeeuw, P., 2011. Differentiating frontostriatal and fronto-cerebellar circuits in attention-deficit/hyperactivity disorder. Biological Psychiatry 69, 1178–1184.

Faraone, S.V., Biederman, J., 2005. What is the prevalence of adult ADHD? Results of a population screen of 966 adults. Journal of Attention Disorders 9, 384–391.

Fusar-Poli, P., Rubia, K., Rossi, G., Sartori, G., Ballotin, U., 2012. Dopamine transporter alterations in ADHD: pathophysiology or adaptation to psychostimulants? A meta-analysis. American Journal of Psychiatry 169, 264–272.

Hart, H., Radua, J., Mataix, D., Rubia, K. Meta-analysis of fMRI studies of inhibition and attention in ADHD: exploring task-specific, stimulant medication and age effects. Archives of General Psychiatry, in press.

Kanwisher, N., Wojciulik, E., 2000. Visual attention: insights from brain imaging. Nature Review Neuroscience 1, 91–100.

Mesulam, M.M., Nobre, A.C., Kim, Y.H., Parrish, T.B., Gitelman, D.R., 2001. Heterogeneity of cingulate contributions to spatial attention. NeuroImage 13, 1065–1072.

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

Nakao, T., Radua, C., Rubia, K., Mataix-Cols, D., 2011. Gray matter volume abnormalities in ADHD and the effects of stimulant medication: voxel-based meta-analysis. American Journal of Psychiatry 168, 1154–1163.

Noreika, V., Falter, C., Rubia, K. Timing deficits in patients with ADHD. Neurospcyhologia, in press.

Plichta, M.M., Vasic, N., Wolf, R.C., Lesch, K.P., Brummer, D., Jacob, C., Fallgatter, A.J., Gron, G., 2009. Neural hyporesponsiveness and hyperresponsiveness during immediate and delayed reward processing in adult attention-deficit/hyperactivity disorder. Biological Psychiatry 65, 7–14.

Radua, J., Mataix-Cols, D., 2009. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. British Journal of Psychiatry 195, 393–402.

Radua, J., Mataix-Cols, D., 2010. Heterogeneity of coordinate-based meta-analyses of neuroimaging data: an example from studies in OCD Reply. British Journal of Psychiatry 197, 77.

Radua, J., Mataix-Cols, D., Phillips, M.L., El-Hage, W., Kronhaus, D.M., Cardoner, N., Surguladze, S. A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps. European Psychiatry, http://dx.doi.org/10.1016/j.eurpsy.2011.04.001, in press.

Radua, J., Via, E., Catani, M., Mataix-Cols, D., 2011. Voxel-based meta-analysis of regional white-matter volume differences in autism spectrum disorder versus healthy controls. Psychological Medicine 41, 1539–1550.

Rubia, K., 2006. The neural correlates of timing functions. In: Glicksohn, J., Myslobodsky, M. (Eds.), Timing the Future: The Case for a Time-Based Prospective Memory. World Scientific Publishing, Hackensack, NJ, pp. 213–238.

Rubia, K., 2011. Cool inferior fronto-striatal dysfunction in attention deficit hyperactivity disorder (ADHD) versus hot ventromedial orbitofronto-limbic dysfunction in conduct disorder: a review. Biological Psychiatry 69, e69–e87.

Rubia, K., Halari, R., Christakou, A., Taylor, E., 2009a. Impulsiveness as a timing disturbance: neurocognitive abnormalities in attention-deficit hyperactivity disorder during temporal processes and normalization with methylphenidate. Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 364, 1919–1931.

Rubia, K., Halari, R., Cubillo, A., Mohammad, M., Taylor, E., 2009b. Methylphenidate normalises activation and functional connectivity deficits in attention and motivation networks in medication-naïve children with ADHD during a Rewarded Continuous Performance Task. Neuropharmacology 57, 640–652.

Rubia, K., Halari, R., Cubillo, A., Smith, A., Mohammad, M., Brammer, M., Taylor, E., 2011a. Methylphenidate normalises fronto-striatal underactivation during interference inhibition in medication-naive boys. Neuropsychopharmacology 36, 1575–1586.

Rubia, K., Halari, R., Taylor, E., Brammer, M., 2011b. Methylphenidate normalises fronto-cingulate underactivation during error processing in children with attention-deficit hyperactivity disorder. Biological Psychiatry 70, 255–262.

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

Rubia, K., Smith, A., 2004. The neural correlates of cognitive time management: a review. Acta Neurobiologiae Experimentalis 64, 329–340.

Rubia, K., Smith, A., Brammer, M., Taylor, E., 2003. Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. NeuroImage 20, 351–358.

Rubia, K., Taylor, E., Smith, A.B., Oksanen, H., Overmeyer, S., Newman, S., 2001. Neuropsychological analyses of impulsiveness in childhood hyperactivity. British Journal of Psychiatry 179, 138–143.

Shaw, P., Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J.P., Greenstein, D., Rapoport, J., 2007. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proceedings of the National Academy of Sciences of the United States of America 104, 19649–21965.

Shaw, P., Malek, M., Watson, B., Sharp, W., Evans, A., Greenstein, D., 2012. Development of cortical surface area and gyrification in attention-deficit/hyperactivity disorder. Biological Psychiatry 72, 191–197.

Shaw, P., Sharp, W.S., Morrison, M., Eckstrand, K., Greenstein, D.K., Clasen, L.S., Evans, A.C., Rapoport, J.L., 2009. Psychostimulant treatment and the developing cortex in attention deficit hyperactivity disorder. American Journal of Psychiatry 166, 58–63.

Smith, A., Giampietro, V., Brammer, M., Taylor, E., Simmons, A.N., Rubia, K., 2011. Progressive functional development of frontostriatoparietal networks during time perception. Human Frontiers in Neuroscience 5, 1–14.

Smith, A.B., Taylor, E., Brammer, M., Halari, R., Rubia, K., 2008. Reduced activation in right lateral prefrontal cortex and anterior cingulate gyrus in medication-naive adolescents with attention deficit hyperactivity disorder during time discrimination. Journal of Child Psychology and Psychiatry 49, 977–985.

Stroup, D.F., Berlin, J.A., Morton, S.C., Olkin, I., Williamson, G.D., Rennie, D., Moher, D., Betsy, J., Becker, B.J., Sipe, T.A., Thacker, S.B., 2000. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. Journal of the American Medical Association 293, 2008–2012.

Toplak, M.E., Dockstader, C., Tannock, R., 2006. Temporal information processing in ADHD: findings to date and new methods. Journal of Neuroscience Methods 151, 15–29.

Valera, E.M., Faraone, S.V., Murray, K.E., Seidman, L.J., 2007. Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. Biological Psychiatry 61, 1361–1369.

Valera, E.M., Spencer, R.M.C., Zeffiro, T.A., Makris, N., Spencer, T.J., Faraone, S.V., Biederman, J., Seidman, L.J., 2010. Neural substrates of impaired sensorimotor timing in adult attention-deficit/hyperactivity disorder. Biological Psychiatry 68, 359–367.

Via, E., Radua, J., Cardoner, N., Happe, F., Mataix-Cols, D., 2011. Meta-analysis of gray matter abnormalities in autism spectrum disorder should Asperger disorder be subsumed under a broader umbrella of autistic spectrum disorder? Archives of General Psychiatry 68, 409–418.

Vloet, T.D., Gilsbach, S., Neufang, S., Fink, G.R., Herpertz-Dahlmann, B., Konrad, K., 2010. Neural mechanisms of interference control and time discrimination in attention-deficit/hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry 49, 356–367.

Weissman, D.H., Roberts, K.C., Visscher, K.M., Woldorff, M.G., 2006. The neural bases of momentary lapses in attention. Nature Neuroscience 9, 971–978.

Wiener, M., Turkeltaub, P., Coslett, H.B., 2010a. The image of time: a voxel-wise meta-analysis. NeuroImage 49, 1728–1740.

Wiener, M., Turkeltaub, P.E., Coslett, H.B., 2010b. Implicit timing activates the left inferior parietal cortex. Neuropsychologia 48, 3967–3971.

Willcutt, E.G., Doyle, A.E., Nigg, J.T., Faraone, S.V., Pennington, B.F., 2005. Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. Biological Psychiatry 57, 1336–1346.

Wittmann, M., Leland, D.S., Paulus, M.P., 2007. Time and decision making: differential contribution of the posterior insular cortex and the striatum during a delay discounting task. Experimental Brain Research 179, 643–653.