Response Inhibition and Reward Anticipation in Medication-Naïve Adults With Attention-Deficit/Hyperactivity Disorder: A Within-Subject Case-Control Neuroimaging Study

Susana Carmona,^{1*} Elseline Hoekzema,^{1*} J. Antoni Ramos-Quiroga,^{1,2}
Vanessa Richarte,² Clara Canals,¹ Rosa Bosch,^{1,2} Mariana Rovira,³
Juan Carlos Soliva,¹ Antonio Bulbena,⁴ Adolf Tobeña,¹ Miguel Casas,^{1,2}
and Oscar Vilarroya^{1,5}

¹*Departament de Psiquiatria i Medicina Legal, Universitat Autònoma de Barcelona, Bellaterra, Spain*

²*Servei de Psiquiatria, Hospital Vall d'Hebron, Barcelona, Spain*

³*CRC Corporacio Sanitaria, Barcelona, Spain*

⁴*Institut de Neuropsiquiatria i Adiccions, Hospital del Mar, Parc de Salut Mar, Barcelona, Spain*

⁵*Fundació IMIM, Barcelona, Spain*

Abstract: Background: Previous research suggests that ADHD patients are characterized by both reduced activity in the inferior frontal gyrus (IFG) during response inhibition tasks (such as the Go-NoGo task), and reduced activity in the ventral striatum during reward anticipation tasks (such as the Monetary-Incentive-Delay [MID] task). However, no prior research has applied either of these paradigms in medication-naïve adults with ADHD, nor have these been implemented in an intrasubject manner. **Methods:** The sample consisted of 19 medication-naïve adults with ADHD and 19 control subjects. Main group analyses were based on individually defined regions of interest: the IFG and the VStr for the Go-NoGo and the MID task respectively. In addition, we analyzed the correlation between the two measures, as well as between these measures and the clinical symptoms of ADHD. **Results:** We observed reduced bilateral VStr activity in adults with ADHD during reward anticipation. No differences were detected in IFG activation on the Go-NoGo paradigm. Correlation analyses suggest that the two tasks are independent at a neural level, but are related behaviorally in terms of the variability of the performance reaction time. Activity in the bilateral VStr but not in the IFG was associated negatively with symptoms of hyperactivity/impulsivity. **Conclusions:** Results underline the implication of the reward system in ADHD adult pathophysiology and suggest that frontal abnormalities during

Additional Supporting Information may be found in the online version of this article.

Susana Carmona and Elseline Hoekzema contributed equally to this work.

Contract grant sponsor: Ministerio de Ciencia e Innovación; Contract grant number: SAF200910901; Contract grant sponsor: Ministerio de Educación y Ciencia (Spanish Government).

*Correspondence to: Susana Carmona, Unitat de Recerca en Neurociència Cognitiva, Departament de Psiquiatria i Medicina Legal,

Universitat Autònoma de Barcelona, Campus Bellaterra, 08193 Bellaterra, Barcelona, Spain. E-mail: susannacarmona@gmail.com

Received for publication 14 December 2010; Revised 15 April 2011; Accepted 2 May 2011

DOI: 10.1002/hbm.21368

Published online 8 August 2011 in Wiley Online Library (wileyonlinelibrary.com).

response inhibition performance may not be such a pivotal aspect of the phenotype in adulthood. In addition, our findings point toward response variability as a core feature of the disorder. *Hum Brain Mapp* 33:2350–2361, 2012. © 2011 Wiley Periodicals, Inc.

Key words: accumbens; ADHD; attention-deficit/hyperactivity disorder; inhibition; reward; ventral striatum; inferior frontal gyrus

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD), a syndrome characterized by symptoms of inattention, hyperactivity, and impulsivity, is one of the most prevalent childhood psychiatric disorders (around 5% of children are diagnosed worldwide) [Polanczyk et al., 2007]. Although symptoms commonly tend to improve with age, only a minority of ADHD children attain complete remission in adult life. In fact, a recent 10-year follow-up study indicates that in more than 50% of cases the symptoms persist into adulthood, and around 35% of the pediatric patients still fulfill ADHD diagnostic criteria in adult life [Biederman et al., 2011]. Given the disabling nature of ADHD, it is important to further our understanding of the neural underpinnings of the disorder, particularly in those subjects that do not ameliorate with age.

Based mostly on studies of children with ADHD, current accounts of the disorder, such as the multiple pathway model [Sonuga-Barke et al., 2010], propose the implication of at least two relatively independent-but not mutually exclusive-ADHD endophenotypes: those characterized by disruptions in executive functions, especially poor inhibition control, and those characterized by abnormalities in the motivational system, particularly in relation to reward anticipation. Whereas executive functions are presumably subserved by dopaminergic networks connecting the dorsal striatum with the lateral and dorsolateral prefrontal cortex, reward management is thought to be mediated by dopaminergic circuits linking the ventral striatum to the orbitofrontal, medial prefrontal, and cingulate cortices [Haber et al., 2010].

Previous functional magnetic resonance imaging (fMRI) studies of ADHD have predominantly focused on the assessment of executive functions, in particular response inhibition, which is often addressed using the Go-NoGo task. This paradigm has been shown to rely on inferior frontal functioning in the healthy population, and ADHD imaging studies have consistently found hypoactivation in this region during the childhood phase of the disorder [see Aron et al., 2003 for a review Aron et al., 2005]. Recently, motivational paradigms have been introduced into ADHD research to investigate the neural bases of reward management. In particular, the Monetary Incentive Delay (MID) task—known to target reward-related regions such as the ventral striatum (VStr)—has been used by different groups to study motivational processes in ADHD. To date, the few studies assessing reward anticipation in

ADHD have reported reduced recruitment of the VStr in both child and adult patients as compared to control subjects [Plichta et al., 2009; Scheres et al., 2007; Strohle et al., 2008], and nearly all such studies have observed a negative association between VStr activation and hyperactive/impulsive symptoms [Scheres et al., 2007; Strohle et al., 2008].

Although both the Go-NoGo and the MID tasks have previously been applied in ADHD research, no studies have implemented the two paradigms in an intrasubject manner. The intrasubject application of the two tasks is important to exclude the variability between subjects and between studies, and consequently discern the weight of each of the processes in the pathophysiology of the disorder. In addition, the assessment of the two processes in the same subjects is specifically relevant in the case of ADHD because it will allow us to evaluate whether these domains are neurally and behaviorally independent as proposed by current accounts of the disorder [Sonuga-Barke et al., 2010].

Furthermore, to our knowledge, no previous fMRI studies have applied either of these tasks in adults with ADHD who have never received medication for their condition. Since methylphenidate/atomoxetine administration has been shown to render short-term and long-term synaptic, structural, and functional changes in key regions for these processes, namely the IFG [Chamberlain et al., 2009; Shaw et al., 2009] and VStr [Kim et al., 2009; Leo et al., 2009], the assessment of medication-naïve patients is essential to relate IFG and VStr alterations to the neurobiology of the disorder.

In the present study, we aim to assess whether medication-naïve adults with ADHD exhibit behavioral and neural disturbances in both response inhibition and reward anticipation. Additionally, we want to evaluate if these disturbances are independent of each other, and to assess if they are associated with clinical symptoms of hyperactivity-impulsivity and inattention as extracted from the Conners Adult ADHD Rating Scale-Self-Rating Form: Long (CAARS) [Conners et al., 1999].

On the basis of preceding studies of ADHD children, we hypothesize that: (a) unmedicated adults with ADHD will show deficient IFG activation during response inhibition and deficient VStr activation during reward anticipation; (b) the neural and behavioral deficits observed in each of the domains will be uncorrelated; and c) the degree of activation in the IFG and VStr will negatively correlate with measures of ADHD clinical severity.

TABLE I. Clinical and demographic data

	ADHD <i>N</i> = 19 mean (SD)	Controls <i>N</i> = 19 mean (SD)	<i>T</i> -value	<i>P</i> value
Age	33.58 (10.3)	29.36 (7.84)	1.41	0.165
Estimated IQ (vocabulary and block-design)	10.94 (2.37)	11.71 (1.52)	1.18	0.247
Clinical data				
WURS	54.15 (17.63)	15.55 (15.24)	7.11	<0.001
ADHD rating scale	35 (8.64)	6.21 (5.85)	12.02	<0.001
CAARS				
A) Memory problems	23.21 (6.84)	5.11 (3.46)	10.29	<0.001
B) Hyperactivity/restlessness	23.05 (7.42)	6.37 (3.91)	8.67	<0.001
C) Impulsivity/emotional lability	19.16 (7.44)	3.95 (3.96)	7.86	<0.001
D) Problems with self-concept	10 (3.57)	2.53 (2.318)	7.64	<0.001
E) DSM-IV inattentive symptoms	19.26 (4.63)	3.12 (2.85)	12.05	<0.001
F) DSM-IV hyperactive-impulsive symptoms	18.41 (4.71)	3.68 (3.27)	10.67	<0.001
G) DSM-IV total ADHD symptoms	37.21 (8.41)	8.11 (5.88)	12.37	<0.001
H) ADHD index	20.79 (6.43)	5 (4.39)	8.83	<0.001

Abbreviations: ADHD (Attention-Deficit/Hyperactivity Disorder); DSM-IV (Diagnostic and Statistical Manual of Mental Diseases, fourth edition), CAARS (Conners Adult ADHD Rating Scale self-rating, form: Long), IQ (Intelligence Quotient), WAIS (Wechsler Adult Intelligence Scale), WURS (Wender Utah Rating Scale).

*This table shows demographic and clinical data of ADHD and control subjects. Variables are expressed by their mean and their standard deviation (SD). In the case of IQ estimation based on Vocabulary and Block-design [(Vocabulary typical score + Block-design typical score)/2] the mean and standard deviation of the population is 10 and 3 respectively.

METHODS AND MATERIALS

Participants

Forty-six right-handed adult males (23 with ADHD and 23 healthy controls) were included in the study, recruited over a three-year period. For neurological reasons, one ADHD and one control subject had to be excluded. Six more subjects (three ADHD and three controls) were omitted from the analysis, due to problems understanding the tasks or to other complications occurring in either of the fMRI paradigms. A team of psychologists and psychiatrists from Vall d'Hebron Hospital carefully evaluated all subjects in order to exclude comorbidity with other psychiatric or personality disorders (as assessed by the Structured Clinical Interview for Axis I (SCID-I) [First et al., 1994] and Axis II (SCID-II) [First et al., 1997]. Subjects who met diagnostic criteria for substance use disorder (abuse/dependence) of tobacco or cannabis within the last 6 months, as well as those with a life history of severe drug consumption (cocaine, heroin, synthetic drugs), were also excluded. Only those subjects with an IQ within one standard deviation from the mean (as estimated by block-design and vocabulary subtests of the Wechsler Adult Intelligence Scale (WAIS-III) [Wechsler, 1977] were included in the study.

All subjects fulfilled the diagnostic criteria for ADHD combined subtype and had never received any pharmacological treatment for their condition. ADHD diagnosis was based on the Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition, Test Revised (DSM-IV TR) [American Psychiatric Association, 2000]. Additional assessment instruments to confirm the diagnosis were the Conners Adult ADHD Diagnostic Interview for DSM-IV

(CAADID) [Epstein et al., 1999], the Wender Utah Rating Scale (WURS) [Ward et al., 1993], the ADHD Rating Scale [DuPaul, 1998] and the CAARS. Only those subjects whose ADHD symptomatology was present before seven years of age were included.

The study was approved by the Hospital Universitari Vall d'Hebron Ethics Committee, and informed consent was obtained from the subjects prior to their participation in the study. Clinical and demographic data of the sample are depicted in Table I.

fMRI Acquisition Parameters

The MRI images were obtained in a GE 1.5T scanner, equipped with a standard quadrature radiofrequency coil. A vacuum pillow was placed inside the coil in order to restrict the subject's head movement. For anatomical reference, a T1-weighted pulse sequence was employed with the following parameters: TR 11.5, TE 4.2, matrix $256 \times 256 \times 96$, FA 15, slice thickness 1.6. Functional volumes were acquired using a T2*-weighted gradient echo sequence. For the *MID* task, the acquisition parameters were: TR = 3,000 ms; TE = 60 ms, FA = 90°, FOV = 30 cm, GAP = 0.5 and a matrix size of $64 \times 64 \times 30$. The *Go-NoGo* paradigm was acquired using the following parameters: TR = 2,275 ms, TE = 60 ms, FA = 90°, FOV = 30 cm, GAP = 0.5 and a matrix size of $64 \times 64 \times 23$.

fMRI Procedure

During the fMRI acquisition, the subjects participated in two event-related fMRI paradigms. The order of presentation was counterbalanced across subjects.

The Go-NoGo task was similar to the ones used in previous studies comprising the presentation of individual letters on a screen [Durstun et al., 2002, 2003; Forman et al., 2004; Menon et al., 2001; Tamm et al., 2002, 2003, 2004; Vollm et al., 2004]. The subjects were instructed to press the button when a letter appeared (go trials), but withhold their response when an “X” was presented (no-go trials). The stimulus duration was 250 ms, and each stimulus was followed by a random inter-stimulus interval between 1,000 and 2,000 ms. The total number of trials, on average, was 225. The percentage of go trials was set to 70% [Durstun et al., 2002, 2003; Tamm et al., 2004]. A higher percentage of go trials relative to no-go trials has been demonstrated to enhance the MRI signal for the no-go trials, by increasing the preponderance of the press response and consequently the difficulty of inhibiting it [Durstun et al., 2002, 2003].

To assess reward anticipation, we used a version of the MID task similar to those employed in previous studies [Scheres et al., 2007; Strohle et al., 2008]. For this task, trials involved the presentation of a cue for 350 ms, followed by a variable delay of between 2,000 and 2,500 ms, and then a target with a duration of between 90 and 650 ms. The subjects were required to press the button before the target disappeared from the screen; target duration was adjusted to produce success in around 66% of the cases (short target duration between 90 and 120 ms; long target duration between 550 and 650 ms). The cues comprised symbolic signs indicating trials with the possibility to win money (+1/+2 euro), to lose money (−1/−2 euro), or to keep the same amount regardless of the performance (control trials). The total number of trials averaged 150, and each of the five conditions (+1/+2/−1/−2/control) was presented for 20% of the trials. The target was followed by a delay (500 ms) and then a feedback screen (1,200 ms), depicting the amount gained or lost by the subject in this trial and the total quantity earned so far. See Supporting Information for a detailed description of the task and the timeline of the experimental procedure.

Data Analysis

Functional MRI data was analyzed with SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>) implemented in Matlab 7.8 (<http://www.mathworks.com/>). Given the *a priori* formulated hypotheses regarding the implication of the IFG and the VStr in response inhibition and reward anticipation respectively, the main analyses for each of the processes were constrained to these brain regions. To optimize the inference of neural activation in IFG and VStr regions, the Blood-oxygen-level dependence (BOLD) response was measured on an individual basis from the subject's anatomical space, hereby avoiding the normalization step (see Supporting Information). This is especially relevant for our study, as ADHD has been related to anatomical abnormalities in frontal regions [Hesslinger et al., 2002; Sowell et al.,

2003] as well as to volumetric and shape alterations in the basal ganglia [Qiu et al., 2009], which could potentially introduce a bias when transforming the images into standardized space. For complementary purposes, analyses based on standard ROI methodology are also provided in the Supporting Information.

The main contrasts of interest for the Go-NoGo paradigm and the MID task were “nogo>go” (corresponding to an increased BOLD response for the inhibition cues, as compared to cues requiring a button press) and “win>control” (reflecting increased fMRI signal in response to cues indicating a potential winning trial, as compared to cues indicating a control trial). Beta values for each of these two contrasts were extracted from individual regions of interest (ROIs) using Marsbar (<http://marsbar.sourceforge.net/>), and imported into SPSS (version 16; <http://www.spss.com/>) to perform the corresponding statistical analyses. This ROI analysis methodology has been used previously in other studies [Egner et al., 2005]. See also the Supporting Information for further details about the preprocessing steps and ROI delineation. Group comparisons of behavioral and neural data were analyzed using an analysis of covariance (ANCOVA), in which diagnosis was entered as a fixed factor, and estimated IQ and age as nuisance covariates.

Besides the group comparisons, we also performed correlation analyses to assess if the detected changes in the IFG and VStr BOLD signals were associated with symptoms of inattention and hyperactivity-impulsivity as extracted from the scales E and F, respectively of the CAARS.

In addition, to examine the independence between response inhibition and reward anticipation, we ran correlation analyses on the behavioral and neural measures derived from each of these two domains. These correlation analyses were complemented with visual inspections of the corresponding scatter plots, to ensure that there were no non-monotonous associations between the two domains that could not be captured by the correlation coefficient.

Finally, to complement the ROI analyses, exploratory whole-brain group comparisons were performed. To do so, we introduced the normalization step and re-estimated single-subject models. The main contrasts for each subject were then entered into a second-level ANCOVA (with age and estimated IQ as nuisance variables) to compare the BOLD contrast obtained from ADHD and control subjects across the whole brain. Comparisons were thresholded at a *P*-value below 0.05 FWE-corrected. Results obtained at a more sensitive threshold (*P* < 0.0001 uncorrected) are also reported in the Supporting Information for informative purposes.

RESULTS

Behavioral Data

Our results indicate that, independent of the task, ADHD subjects present a slower reaction time (RT) and a

TABLE II. Behavioral data

	ADHD <i>N</i> = 19 mean (SD)	Controls <i>N</i> = 19 mean (SD)	<i>F</i> statistic df [3,34]	<i>P</i> value
Go-NoGo task (inhibition response)				
Go trials incorrect	7.16 (15.41)	0.37 (0.96)	0.826	0.488
Nogo trials incorrect	24.16 (17.57)	19.58 (12.60)	1.382	0.265
Reaction time	361.37 (70.44)	334.39 (40.32)	3.962	0.016
Standard deviation	74.72 (15.64)	60.75 (12.06)	6.988	0.001
MID task (reward anticipation)				
Percentage correct	63.61 (4.25)	66.51 (3.48)	2.133	0.114
Correct win cue trials	8.57 (5.85)	9.89 (6.12)	1.022	0.395
Correct loss cue trials	24.63 (4.16)	28.52 (5.53)	2.674	0.063
Correct control cue trials	29.57 (1.38)	29.63 (1.8)	0.927	0.438
Reaction time	246.49 (32.89)	205.25 (19.74)	11.33	<0.001
Standard deviation	73.49 (30.41)	48.19 (10.28)	5.2	0.005

This table lists the results of group comparisons on the behavioral measures extracted from the Go-NoGo paradigm and the monetary incentive delay (MID) task after excluding the effect of estimated IQ and age. Variables are expressed by their mean and their standard deviation (SD).

wider RT standard deviation as compared to control subjects (see Table II for behavioral group comparisons). According to the behavioral measures extracted from the Go-NoGo task, ADHD subjects did not differ from the control subjects with regard to the number of incorrectly omitted responses on go trials (“go trials incorrect”) or the number of incorrect button presses on nogo trials (“nogo trial incorrect”). With regard to the measures extracted from the MID task, the analyses of covariance rendered no significant differences between the ADHD and the control group in the percentage of in-time button presses while the target was on the screen (“percentage correct”), independent of whether this target was preceded by a win cue (“correct win cue trials”), a loss cue (“correct loss cue trials”) or a control cue (“correct control cue trials”).

IFG and VStr ROI Analyses

We did not observe significant group differences in the beta values extracted from the left or right IFG region for the response inhibition task. However, we found decreased activation in bilateral VStr during reward anticipation in the ADHD group as compared to the control

group (see Table III and Fig. 1). To exclude the potential influence of one of the processes over the other, we repeated the group comparisons for each of the regions after covarying out the effect of the other region. Importantly, VStr activity persisted after accounting for the effect of IFG activity (left VStr, $F[5,32] = 2.753$, $P = 0.035$; right VStr: $F[5,32] = 2.515$, $P = 0.049$); however, no significant differences emerged in IFG activity when controlling for the effect of VStr activity (left IFG, $F[5,32] = 0.223$, $P = 0.95$; right IFG: $F[5,32] = 0.482$, $P = 0.787$).

Correlation Analyses

No significant associations were observed between the two tasks at a neural level (all P values >0.140 for the whole sample as well as for each of the groups separately). In addition, a visual inspection of the scatter plots confirmed that the level of IFG activation during response inhibition was indeed independent from the level of VStr activation during reward anticipation, since no non-monotonous associations were observed between the variables. Interestingly, when assessing the correlation between the two domains at a behavioral level, our results indicated a

TABLE III. Group comparisons of IFG and VStr beta values

	ADHD <i>N</i> = 19 mean (SD)	Controls <i>N</i> = 19 mean (SD)	<i>F</i> statistic df [3,34]	<i>P</i> value
Inhibition control (NOGO>GO)				
Left inferior frontal gyrus	-0.01 (0.37)	-0.04 (0.42)	0.034	0.991
Right inferior frontal gyrus	0.25 (0.57)	0.33 (0.42)	0.387	0.763
Reward Anticipation (WIN>CONTROL)				
Left ventral striatum	0.59 (1.41)	2.20 (2.69)	4.38	0.010
Right ventral striatum	0.79 (1.71)	2.29 (2.15)	3.72	0.020

This table shows the results of group comparisons of the beta values extracted from the inferior frontal gyrus and the ventral striatum during response inhibition and reward anticipation tasks respectively. Estimated IQ and age were introduced in the model as nuisance covariates. Variables are expressed by their mean and their standard deviation (SD). Boldface values indicate which group comparisons survive Bonferroni correction ($P = 0.012$).

Figure 1.

Beta values extracted from the inferior frontal gyrus (IFG) and the ventral striatum (VStr) during response inhibition and reward anticipation tasks respectively for the ADHD and the control (CTRLS) group. The p values indicated in the table reflect significant group differences as extracted from the ANCOVA. An asterisk above the bar (*) Indicates that the beta value is significantly different from zero, as assessed by one-sample t tests. Error bars represent the standard error of the mean. Abbreviations: L: left, R: right, VStr.

significant association between the Go-NoGo standard deviation and the MID task standard deviation ($r = 0.58$, $P < 0.0001$). This association seems to be produced mainly by the ADHD group ($r = 0.54$, $P = 0.017$) and was not significant when considering only the control group ($P > 0.275$).

Regarding the correlation analyses with clinical data, activation in the bilateral ventral striatum during reward anticipation was negatively associated with symptoms of hyperactivity and impulsivity (left VStr: $r = -0.408$, $P = 0.011$; right VStr: $r = -0.459$, $P = 0.004$) but not with symptoms of inattention (left VStr: $r = -0.26$, $P = 0.11$; right VStr: $r = -0.286$, $P = 0.082$). See Figure 2.

IFG activation during the Go-NoGo did not correlate with any clinical measure (Hyperactivity/Impulsivity: left IFG: $r = 0.056$, $P = 0.741$; right IFG: $r = 0.029$, $P = 0.863$. Inattention: left IFG: $r = 0.137$, $P = 0.411$; right IFG: $r = 0.052$, $P = 0.758$).

It is important to mention that the correlations between VStr activity and clinical measures are only significant when analyzing the sample as a whole (ADHD and control subjects together). No significant associations were detected between neural activation and clinical measures when analyzing the ADHD and the control group separately.

Whole-Brain Group Analyses

Whole-brain analyses also suggested that the MID task is more sensitive to capturing adult ADHD abnormalities than the Go-NoGo task. In particular, second-level analyses

for the “win>control” contrast indicated reduced activation in the ADHD group, as compared to the control group, in the right dorsal anterior midcingulate cortex (daMCC) (BA 24/32; coordinates = $14_x16_y40_z$; $T = 5.85$; $P = 0.041$, FWE-corrected) and in the right supramarginal gyrus (BA 40; coordinates = $42_x-38_y36_z$; $T = 5.85$; $P = 0.022$, FWE-corrected). No significant differences were observed between ADHD and control subjects in the “nogo>go” contrast extracted from the Go-NoGo paradigm. See also the Supporting Information for further whole-brain results.

DISCUSSION

The main objective of our study was to assess the implication of motivational aspects and executive functions in adult patients with ADHD, as well as to analyze if the two processes are independent or interrelated at a behavioral and a neural level. In addition, we aimed to examine the relation between the two processes, and the severity of the clinical symptoms of hyperactivity-impulsivity and inattention.

Although previous studies have already implemented the Go-NoGo and MID task to assess response inhibition and reward anticipations in adults with ADHD, none of these studies have applied the two paradigms in an intra-subject manner.

The results indicate that unmedicated adults with ADHD present deficient neural activity in the bilateral VStr during the anticipation of potential rewards, but do not differ from control subjects in IFG activity when they must inhibit a preponderant motor response. Correlation

Figure 2.

Correlations between left (L) and right (R) VStr activity and clinical ratings of hyperactivity/impulsivity (H-I) according to the self-reports on the Conners-Adult ADHD Rating Scale (CAARS). For illustrative purposes we have displayed separate symbols for each group.

analyses suggest that the two domains are independent in terms of performance accuracy and neural activity, but interrelated in terms of RT variability. In addition, regression analyses with clinical measures suggest that the level of activation of the bilateral VStr during reward anticipation is negatively associated with symptoms of hyperactivity-impulsivity.

The ventral striatum, especially the accumbens nucleus, comprises the main target of mesolimbic-DA innervations from the ventral tegmental area and plays a pivotal role in effective responses to delayed rewards [Schultz, 1998, 2001; Schultz et al., 1997]. Our finding of reduced VStr activation in response to cues that predict potential rewards is in line with neurochemical accounts of ADHD postulating that part of the ADHD symptoms stem either from a generalized hypodopaminergic function [Sagvolden et al., 2005; Sonuga-Barke, 2003] or a specific failure in the transfer of dopaminergic signaling from the reward to its preceding cue [Tripp et al., 2008].

Behavioral studies have provided evidence indicating alterations in reward circuits in patients with ADHD. A recent study, for example, indicates that whereas the proportion of children with pure response inhibition deficits is around 6.4%, more than nineteen percent of ADHD children exclusively present deficits in motivational processes [Sonuga-Barke et al., 2010]. In particular, one of the most consistently reported abnormalities with regard to reward management is the stronger preference of ADHD subjects to choose smaller immediate over larger delayed rewards [Luman et al., 2005]. Interestingly, this atypical response to reinforcement seems to be especially associated with

hyperactive-impulsive symptoms [Scheres et al., 2008; Sonuga-Barke et al., 1992].

Moreover, animal models of ADHD [Russell, 2000, 2003; Russell et al., 2005] as well as lesion studies [Cardinal et al., 2001] provide solid evidence for the implication of the VStr in the etiology of ADHD, especially with regard to the manifestation of hyperactive and impulsive symptoms. In particular, it has been reported that nucleus accumbens lesions in rats produce hyperactive - impulsive behavior [Cardinal et al., 2001] and modulate the effect of methylphenidate on locomotor activity [Podet et al., 2010].

Neuroimaging studies in ADHD patients further support the implication of the VStr in the disorder [Carmona et al., 2009]. For instance, a recent PET study assessing dopaminergic function in medication-naïve adults with ADHD observed a reduced availability of the dopamine transporter as well as of D2 and D3-like receptors in the VStr in the patient with the disorder [Volkow et al., 2009].

Furthermore, all previous fMRI studies that assess reward management using different versions of the *MID* task report hypo-responsiveness of the VStr to cues that signal reward, in both adults [Plichta et al., 2009; Strohle et al., 2008] and children [Scheres et al., 2007] with ADHD. Indeed, in line with our findings, two of these studies also observed a negative correlation between VStr activation and hyperactive/impulsive symptoms [Scheres et al., 2007; Strohle et al., 2008].

Hence, our finding of reduced VStr activation in ADHD dovetails with current neurochemical models of the disorder, as well as with empirical research involving behavioral, lesion and neuroimaging studies.

With regard to IFG activity, compelling evidence indicates reduced activation of this region during response inhibition in ADHD children and adolescents, as measured by the “nogo>go” contrast on the Go-NoGo paradigm [Aron et al., 2005]. However, contrary to our predictions, in the present study we did not encounter a significant reduction of IFG activity in adults with ADHD during the inhibition response, nor did we observe significant group differences in behavioral performance. Furthermore, we did not find any significant correlation between IFG activity and clinical measures nor group differences in the whole-brain comparisons of the Go-NoGo task.

Despite the neuropsychological heterogeneity that characterizes ADHD, most of the behavioral studies performed in children with the disorder are consistent in documenting the presence of abnormalities in response inhibition. In contrast, studies in adult populations have provided highly inconsistent results. Although some studies report deficits in behavioral inhibition in adults with ADHD [Aron et al., 2003; Hervey et al., 2004], some others find no differences in performance [see for example Banich et al., 2009; Clark et al., 2007; Muller et al., 2007]. Interestingly, there are various studies that report group differences only with regard to omission errors, but not to commission errors [e.g., McLoughlin et al., 2010; Tucha et al., 2008; Rapport et al., 2001]. Moreover, in accordance with our results other studies observe differences in mean reaction time and reaction time variability, but not in accuracy of performance [e.g., Chamberlain et al., 2007; Epstein et al., 2001].

To date, only a few fMRI studies have assessed response inhibition in adults with ADHD. In line with neuropsychological data, previous studies that applied a Go-NoGo paradigm to evaluate response inhibition in adults with ADHD have rendered inconsistent results, reporting either no differences [Dillo et al., 2010], increases [Dibbets et al., 2009; Kooistra et al., 2010], or decreases [Epstein et al., 2007] in IFG recruitment when comparing the control and patient groups.

The use of mixed samples including men and women diagnosed with different ADHD subtypes can contribute to the discrepancy between findings [see Dillo et al., 2010; Epstein et al., 2007]. In addition, it should be noted, that none of previous studies accounted for the potential confounding variable of previous medication exposure, which is known to affect IFG recruitment in response inhibition tasks [Chamberlain et al., 2009].

Moreover, besides the potential effect of sample differences, a detailed comparison among these studies suggests that the discordant findings could also stem from differences in the rate of stimulus presentation and the contrast used to perform group comparisons. Whereas most of the studies, including ours, use a relatively short inter-stimulus-interval on the Go-NoGo paradigm [Aron et al., 2005], Kooistra et al. assessed group differences using both a fast and a slow event rate Go-NoGo task [Kooistra et al., 2010]. The authors did not observe group differences in IFG ac-

tivity when the stimuli were presented at a fast rate but did find increased IFG activation in the ADHD group as compared to the control group when the stimuli were presented at a slow rate. The use of different contrasts to assess group differences also seems to contribute to the discrepancies in the available literature on this topic. The increased IFG activation in ADHD subjects reported in Dibbets’ study results from comparing the brain response elicited during the noGo trials between the two groups [Dibbets et al., 2009]. The authors explicitly state that no group differences were detected when contrasting brain activation associated with response inhibition, that is, when comparing groups on the “noGo>Go” contrast. Likewise, the reduced IFG activity observed in Epstein’s study is the result of group comparisons on brain activity during the noGo trials. No results are reported in Epstein’s study with regard to group comparisons on the “noGo>Go” contrast [Epstein et al., 2007].

Hence, whereas IFG hypo-responsiveness on the Go-NoGo task is a highly consistent finding in ADHD children, our results, alongside evidence derived from previous studies, suggest that this is not the case in the adult form of the disorder. This hints at the possibility that developmental aspects modulate the implication of IFG and response inhibition deficits in the neurobiology of ADHD.

Recently, the trajectory of the disease across the life-span has received more attention. Developmental accounts of ADHD postulate that, whereas subcortical dysfunctions manifest early in life and persist irrespective of symptom adaptation, deficits in frontal regions, which develop throughout childhood and adolescence, are related to the extent to which an individual can effortfully compensate for striatal dysfunctions [Halperin et al., 2006, 2008].

Several longitudinal studies have been undertaken to evaluate the neurobiological basis of persistent and remittent ADHD symptomatology, showing a divergent progression of the neural alterations accompanying the disorder as a function of the clinical outcome. Some of these studies suggest that certain neural alterations observed in ADHD children, especially those affecting the prefrontal cortex, are produced by a delay in cortical maturation rather than by a complete deviation from normality [McLaughlin et al., 2010; Shaw et al., 2007]. Moreover, an fMRI study assessing the implication of maturational processes in ADHD hypofrontality on tasks of response inhibition demonstrated a normalization of IFG activation from adolescence to adulthood [Rubia et al., 2000].

On the basis of these results, we postulate that the absence of IFG deficits in adults with ADHD observed in the current study may reflect the maturation of this region with age. However, more fMRI longitudinal studies assessing the progression of response inhibition deficits from childhood to adulthood need to be performed to establish whether the related hypoactivation in this region normalizes with age.

Alongside ROI data, whole-brain analyses support the differential contribution of motivational and executive

functions to adult ADHD. Whereas group comparisons rendered no differences on the *Go-NoGo* task, we observed reduced activation in the patient group in the right daMCC and right supramarginal gyrus during reward anticipation. See Supporting Information for an interpretation and integration of those findings with previous literature.

At a behavioral level, group comparisons show that ADHD subjects do not significantly differ from control subjects on measures of accuracy, but present a significantly slower RT with a wider variation independent of the task they are performing. The finding of slower and more variable RT in ADHD subjects is consistent with previous literature. In fact, increased response variability is commonly regarded as one of the most consistent manifestations of the disorder [Castellanos et al., 2006] and as one of the better indices to predict diagnostic severity and altered functioning [Rubia et al., 2007a,b]. Indeed, a recent sibling-pair study in children and adolescents with ADHD observed that measures of RT (mean RT and RT standard deviation) could explain 85% of the familial variance of ADHD, whereas accuracy measures (in particular commission and omission error on the *Go-NoGo* task) only reflected 13% of the familial variance of the disorder [Kuntsi et al., 2010]. According to these authors it is possible that abnormalities in reaction time represents the core enduring deficits directly linked to the etiology of ADHD, whereas performance errors represent a prefrontally mediated executive control dysfunction linked to persistence or desistence of ADHD during adolescence. Interestingly, a larger variability in performance has been postulated to result from changes in the degree of motivation, and has been observed to correlate with key regions of the reward circuit such as the medial prefrontal cortex and the VStr in adult ADHD [Depue et al., 2010].

One of the strengths of the study is the assessment of the two tasks within the same subjects, which allowed us not only to discern the weight of each of the two processes but also to evaluate the independency between them. The multiple pathway model proposed by Sonuga-Barke explains the ADHD neuropsychological heterogeneity in terms of independent cognitive and motivational deficits grounded on discrete neural circuits [Sonuga-Barke, 2003; Solanto et al., 2001]. Several neuropsychological studies have demonstrated the dissociation between response inhibition and motivational deficits [Sonuga-Barke et al., 2010; Solanto et al., 2001], however, to our knowledge, this is the first neuroimaging study that directly tests and supports the neural segregation of the two processes. Our findings provide preliminary evidence that response inhibition and reward anticipation constitute two distinct impairments underpinned by differentiated neural pathways. In particular, the between-task correlation analyses indicate that accuracy and neural measures for the *Go-NoGo* task are dissociable from those extracted from the MID task. In addition, the reported group differences in VStr activity persist after excluding the potential contribu-

tion of IFG and the absence of IFG group differences did not emerge after covarying out the effect of VStr activation, which further indicates that two processes represent distinct neural pathways of impairment in ADHD.

Nevertheless, we observed that measures of RT variability are significantly correlated across the two tasks. That is, those subjects with higher RT variability in the *Go-NoGo* task also present higher RT variability in the MID task.

Taken together, behavioral group comparisons and between-task correlations suggest that, although the two processes seem to be dissociable in terms of performance accuracy and neural activity, response variability is a common feature of ADHD that is manifested across different domains.

This study presents some limitations that must be considered. First of all, the selectivity of the sample, although improving the internal validity of the study, can also bias its representativeness. Adult cases of ADHD that have never received medication represent a relatively small percentage of the ADHD population. Furthermore, our participants were also carefully screened for co-morbidity with other psychiatric disorders known to frequently co-occur with ADHD, such as anxiety, depression and drug use/abuse. These conditions have been related to functional alterations in the IFG [Bystritsky et al., 2001; Engels et al., 2010; Karch et al., 2008; Wolfensberger et al., 2008] and the VStr [Balfour, 2009; Drevets et al., 2001; Kalin et al., 2005; Pizzagalli et al., 2009; Sturm et al., 2003; Wacker et al., 2009] and hence represent an important source of bias that needs to be controlled for. However, these strict selection criteria reduce the ecological validity of the sample, compromising its prototypicality for the ADHD adult population. This premise also applies to the handedness, gender, and subtype criteria. We restricted our sample to comprise only right-handed male ADHD patients classified as the combined subtype, hereby excluding ADHD patients with different characteristics that are potentially tied to distinct neurofunctional deficits.

Another important limitation of the study is the fact that motivational aspects and executive functions are intrinsically intertwined. In other words, the degree of motivation for the task modulates the performance on the *Go-NoGo* paradigm, and, in parallel, executive functions such as attention or working memory is also engaged during the MID task. This inherent inter-relation makes it difficult to completely discern the contribution of each of the processes in ADHD.

In summary, our data provide the first neuroimaging evidence that executive functions and motivational processes represent dissociable deficits in ADHD. Moreover, our findings indicate that medication-naïve adults with ADHD exhibit neurofunctional signs of altered reward processing, but do not differ from controls in the degree of brain activity during response inhibition. These findings stress the relevance of reward brain circuits in adult ADHD, but suggest that abnormalities in response

inhibition may not be such a pivotal aspect of the phenotype in adulthood, potentially reflecting a delayed maturation of the prefrontal cortex. Finally, our results provide support for intrasubject variability as a key feature of ADHD that is manifested across different domains.

REFERENCES

- American Psychiatric Association (2000) Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, Washington, DC, American Psychiatric Association.
- Aron AR, Poldrack RA (2005): The cognitive neuroscience of response inhibition: Relevance for genetic research in attention-deficit/hyperactivity disorder. *Biol Psychiatry* 57:1285–1292.
- Aron AR, Dowson JH, Sahakian BJ, Robbins TW (2003): Methylphenidate improves response inhibition in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry* 54:1465–1468.
- Balfour DJ (2009): The neuronal pathways mediating the behavioral and addictive properties of nicotine. *Handb Exp Pharma* 192:209–233.
- Banich MT, Burgess GC, Depue BE, Ruzic L, Bidwell LC, Hitt-Laustsen S, Du YP, Willcutt EG (2009): The neural basis of sustained and transient attentional control in young adults with ADHD. *Neuropsychologia* 47:3095–3104.
- Biederman J, Petty CR, Clarke A, Lomedico A, Faraone SV (2011): Predictors of persistent ADHD: An 11-year follow-up study. *J Psychiatr Res* 45:150–155.
- Bystritsky A, Pontillo D, Powers M, Sabb FW, Craske MG, Bookheimer SY (2001): Functional MRI changes during panic anticipation and imagery exposure. *Neuroreport* 12:3953–3957.
- Cardinal RN, Pennicott DR, Sugathapala CL, Robbins TW, Everitt BJ (2001): Impulsive choice induced in rats by lesions of the nucleus accumbens core. *Science* 292:2499–2501.
- Carmona S, Proal E, Hoekzema EA, Gispert JD, Picado M, Moreno I, Soliva JC, Bielsa A, Rovira M, Hilferty J, Bulbena A, Casas M, Tobena A, Vilarroya O (2009): Vento-striatal reductions underpin symptoms of hyperactivity and impulsivity in attention-deficit/hyperactivity disorder. *Biol Psychiatry* 66:972–977.
- Castellanos FX, Sonuga-Barke EJ, Milham MP, Tannock R (2006): Characterizing cognition in ADHD: Beyond executive dysfunction. *Trends Cogn Sci* 10:117–123.
- Chamberlain SR, Del CN, Dowson J, Muller U, Clark L, Robbins TW, Sahakian BJ (2007): Atomoxetine improved response inhibition in adults with attention deficit/hyperactivity disorder. *Biol Psychiatry* 62:977–984.
- Chamberlain SR, Hampshire A, Muller U, Rubia K, Del CN, Craig K, Regenthal R, Suckling J, Roiser JP, Grant JE, Bullmore ET, Robbins TW, Sahakian BJ (2009): Atomoxetine modulates right inferior frontal activation during inhibitory control: A pharmacological functional magnetic resonance imaging study. *Biol Psychiatry* 65:550–555.
- Clark L, Blackwell AD, Aron AR, Turner DC, Dowson J, Robbins TW, Sahakian BJ (2007): Association between response inhibition and working memory in adult ADHD: A link to right frontal cortex pathology? *Biol Psychiatry* 61:1395–1401.
- Conners CK, Erhardt D, Sparrow E (1999): Conners' Adult ADHD Rating Scales (CAARS), Technical Manual. Toronto: Multi-Health Systems.
- Depue BE, Burgess GC, Willcutt EG, Bidwell LC, Ruzic L, Banich MT (2010): Symptom-correlated brain regions in young adults with combined-type ADHD: Their organization, variability, and relation to behavioral performance. *Psychiatry Res* 182:96–102.
- Dibbets P, Evers L, Hurks P, Marchetta N, Jolles J (2009): Differences in feedback- and inhibition-related neural activity in adult ADHD. *Brain Cogn* 70:73–83.
- Dillo W, Goke A, Prox-Vagedes V, Szyzik GR, Roy M, Donnerstag F, Emrich HM, Ohlmeier MD (2010): Neuronal correlates of ADHD in adults with evidence for compensation strategies—A functional MRI study with a Go/No-Go paradigm. *Ger Med Sci* 8:Doc09.
- Drevets WC, Gautier C, Price JC, Kupfer DJ, Kinahan PE, Grace AA, Price JL, Mathis CA (2001): Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. *Biol Psychiatry* 49:81–96.
- DuPaul GJ (1998): ADHD Rating Scale-IV: Checklists, Norms, and Clinical Interpretation, Vol. 8. New York: Guilford Press. pp 79.
- Durstun S, Thomas KM, Worden MS, Yang Y, Casey BJ (2002): The effect of preceding context on inhibition: An event-related fMRI study. *Neuroimage* 16:449–453.
- Durstun S, Tottenham NT, Thomas KM, Davidson MC, Eigsti IM, Yang Y, Ulug AM, Casey BJ (2003): Differential patterns of striatal activation in young children with and without ADHD. *Biol Psychiatry* 53:871–878.
- Egner T, Hirsch J (2005): Cognitive control mechanisms resolve conflict through cortical amplification of task-relevant information. *Nat Neurosci* 8:1784–1790.
- Engels AS, Heller W, Spielberg JM, Warren SL, Sutton BP, Banich MT, Miller GA (2010): Co-occurring anxiety influences patterns of brain activity in depression. *Cogn Affect Behav Neurosci* 10:141–156.
- Epstein JN, Johnson DE, Varia IM, Conners CK (2001): Neuropsychological assessment of response inhibition in adults with ADHD. *J Clin Exp Neuropsychol* 23:362–371.
- Epstein JN, Casey BJ, Tonev ST, Davidson MC, Reiss AL, Garrett A, Hinshaw SP, Greenhill LL, Glover G, Shafritz KM, Vitolo A, Kotler LA, Jarrett MA, Spicer J (2007): ADHD- and medication-related brain activation effects in concordantly affected parent-child dyads with ADHD. *J Child Psychol Psychiatry* 48:899–913.
- Epstein JN, Johnson DE, Conners CK (1999). Conners Adult ADHD Diagnostic Interview for DSM-IV. North Tonawanda, NY, Multi-Health Systems.
- First M, Spitzer R, Williams BW (1994): Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P), Version 2. New York, New York State Psychiatric Institute.
- First M, Gibbon M, Spitzer R, Williams BW, Benjamin LS (1997): Interview for DSM-IV Axis II Personality Disorders SCID-II. Washington, DC, American Psychiatric Press.
- Forman SD, Dougherty GG, Casey BJ, Siegle GJ, Braver TS, Barch DM, Stenger VA, Wick-Hull C, Pizarov LA, Lorensen E (2004): Opiate addicts lack error-dependent activation of rostral anterior cingulate. *Biol Psychiatry* 55:531–537.
- Haber SN, Knutson B (2010): The reward circuit: Linking primate anatomy and human imaging. *Neuropsychopharmacology* 35:4–26.
- Halperin JM, Schulz KP (2006): Revisiting the role of the prefrontal cortex in the pathophysiology of attention-deficit/hyperactivity disorder. *Psychol Bull* 132:560–581.

- Halperin JM, Trampush JW, Miller CJ, Marks DJ, Newcorn JH (2008): Neuropsychological outcome in adolescents/young adults with childhood ADHD: Profiles of persisters, remitters and controls. *J Child Psychol Psychiatry* 49:958–966.
- Hervey AS, Epstein JN, Curry JF (2004): Neuropsychology of adults with attention-deficit/hyperactivity disorder: A meta-analytic review. *Neuropsychology* 18:485–503.
- Hesslinger B, Tebartz van EL, Thiel T, Haegele K, Hennig J, Ebert D (2002): Frontoorbital volume reductions in adult patients with attention deficit hyperactivity disorder. *Neurosci Lett* 328:319–321.
- Hoekzema E, Carmona S, Ramos-Quiroga JA, Richarte V, Picado M, Bosch R, Rovira M, Soliva JC, Bulbena A, Tobeña A, Casas M, Vilarroya O (2011): Neural network dysregulation during rest in ADHD: An independent components and functional connectivity study. In preparation.
- Kalin NH, Shelton SE, Fox AS, Oakes TR, Davidson RJ (2005): Brain regions associated with the expression and contextual regulation of anxiety in primates. *Biol Psychiatry* 58:796–804.
- Karch S, Jager L, Karamatskos E, Graz C, Stammel A, Flatz W, Lutz J, Holtschmidt-Taschner B, Genius J, Leicht G, Pogarell O, Born C, Moller HJ, Hegerl U, Reiser M, Soyka M, Mulert C (2008): Influence of trait anxiety on inhibitory control in alcohol-dependent patients: Simultaneous acquisition of ERPs and BOLD responses. *J Psychiatr Res* 42:734–745.
- Kim Y, Teylan MA, Baron M, Sands A, Nairn AC, Greengard P (2009): Methylphenidate-induced dendritic spine formation and DeltaFosB expression in nucleus accumbens. *Proc Natl Acad Sci USA* 106:2915–2920.
- Kooistra L, van der Meere JJ, Edwards JD, Kaplan BJ, Crawford S, Goodyear BG (2010): Preliminary fMRI findings on the effects of event rate in adults with ADHD. *J Neural Transm* 117:655–662.
- Kuntsi J, Wood AC, Rijdsdijk F, Johnson KA, Andreou P, Albrecht B, rias-Vasquez A, Buitelaar JK, McLoughlin G, Rommelse NN, Sergeant JA, Sonuga-Barke EJ, Uebel H, van der Meere JJ, Banaschewski T, Gill M, Manor I, Miranda A, Mulas F, Oades RD, Roeyers H, Rothenberger A, Steinhausen HC, Faraone SV, Asherson P (2010): Separation of cognitive impairments in attention-deficit/hyperactivity disorder into 2 familial factors. *Arch Gen Psychiatry* 67:1159–1167.
- Leo D, Adriani W, Cavaliere C, Cirillo G, Marco EM, Romano E, di PU, Papa M, Perrone-Capano C, Laviola G (2009): Methylphenidate to adolescent rats drives enduring changes of accumbal Htr7 expression: Implications for impulsive behavior and neuronal morphology. *Genes Brain Behav* 8:356–368.
- Luman M, Oosterlaan J, Sergeant JA (2005): The impact of reinforcement contingencies on AD/HD: A review and theoretical appraisal. *Clin Psychol Rev* 25:183–213.
- McLoughlin G, Albrecht B, Banaschewski T, Rothenberger A, Brandeis D, Asherson P, Kuntsi J (2010): Electrophysiological evidence for abnormal preparatory states and inhibitory processing in adult ADHD. *Behav Brain Funct* 6:66.
- McLaughlin KA, Fox NA, Zeanah CH, Sheridan MA, Marshall P, Nelson CA (2010): Delayed maturation in brain electrical activity partially explains the association between early environmental deprivation and symptoms of attention-deficit/hyperactivity disorder. *Biol Psychiatry* 68:329–336.
- Menon V, Adelman NE, White CD, Glover GH, Reiss AL (2001): Error-related brain activation during a Go/NoGo response inhibition task. *Hum Brain Mapp* 12:131–143.
- Muller BW, Gimbel K, Keller-Pliessnig A, Sartory G, Gastpar M, Davids E (2007): Neuropsychological assessment of adult patients with attention-deficit/hyperactivity disorder. *Eur Arch Psychiatry Clin Neurosci* 257:112–119.
- Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, Dougherty DD, Iosifescu DV, Rauch SL, Fava M (2009): Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *Am J Psychiatry* 166:702–710.
- Plichta MM, Vasic N, Wolf RC, Lesch KP, Brummer D, Jacob C, Fallgatter AJ, Gron G (2009): Neural hypo-responsiveness and hyper-responsiveness during immediate and delayed reward processing in adult attention-deficit/hyperactivity disorder. *Biol Psychiatry* 65:7–14.
- Podet A, Lee MJ, Swann AC, Dafny N (2010): Nucleus accumbens lesions modulate the effects of methylphenidate. *Brain Res Bull* 82:293–301.
- Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA (2007): The worldwide prevalence of ADHD: A systematic review and meta-regression analysis. *Am J Psychiatry* 164:942–948.
- Qiu A, Crocetti D, Adler M, Mahone EM, Denckla MB, Miller MI, Mostofsky SH (2009): Basal ganglia volume and shape in children with attention deficit hyperactivity disorder. *Am J Psychiatry* 166:74–82.
- Rapport LJ, Van VA, Tzelepis A, Friedman SR (2001): Executive functioning in adult attention-deficit hyperactivity disorder. *Clin Neuropsychol* 15:479–491.
- Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SC, Simmons A, Andrew C, Bullmore ET (2000): Functional frontalization with age: Mapping neurodevelopmental trajectories with fMRI. *Neurosci Biobehav Rev* 24:13–19.
- Rubia K, Smith A, Taylor E (2007a) Performance of children with attention deficit hyperactivity disorder (ADHD) on a test battery of impulsiveness. *Child Neuropsychol* 13:276–304.
- Rubia K, Smith AB, Brammer MJ, Taylor E (2007b) Temporal lobe dysfunction in medication-naïve boys with attention-deficit/hyperactivity disorder during attention allocation and its relation to response variability. *Biol Psychiatry* 62:999–1006.
- Russell VA (2000): The nucleus accumbens motor-limbic interface of the spontaneously hypertensive rat as studied in vitro by the superfusion slice technique. *Neurosci Biobehav Rev* 24:133–136.
- Russell VA (2003): Dopamine hypofunction possibly results from a defect in glutamate-stimulated release of dopamine in the nucleus accumbens shell of a rat model for attention deficit hyperactivity disorder—The spontaneously hypertensive rat. *Neurosci Biobehav Rev* 27:671–682.
- Russell VA, Sagvolden T, Johansen EB (2005): Animal models of attention-deficit hyperactivity disorder. *Behav Brain Funct* 1:9.
- Sagvolden T, Johansen EB, Aase H, Russell VA (2005): A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. *Behav Brain Sci* 28:397–419.
- Scheres A, Milham MP, Knutson B, Castellanos FX (2007): Ventral striatal hypo-responsiveness during reward anticipation in attention-deficit/hyperactivity disorder. *Biol Psychiatry* 61:720–724.
- Scheres A, Lee A, Sumiya M (2008): Temporal reward discounting and ADHD: Task and symptom specific effects. *J Neural Transm* 115:221–226.
- Schultz W (1998): Predictive reward signal of dopamine neurons. *J Neurophysiol* 80:1–27.
- Schultz W (2001): Reward signaling by dopamine neurons. *Neuroscientist* 7:293–302.

- Schultz W, Dayan P, Montague PR (1997): A neural substrate of prediction and reward. *Science* 275:1593–1599.
- Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, Clasen L, Evans A, Giedd J, Rapoport JL (2007): Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proc Natl Acad Sci USA* 104:19649–19654.
- Shaw P, Sharp WS, Morrison M, Eckstrand K, Greenstein DK, Clasen LS, Evans AC, Rapoport JL (2009): Psychostimulant treatment and the developing cortex in attention deficit hyperactivity disorder. *Am J Psychiatry* 166:58–63.
- Solanto MV, Abikoff H, Sonuga-Barke EJ, Schachar R, Logan GD, Wigal T, Hechtman L, Hinshaw S, Turkel E (2001): The ecological validity of delay aversion and response inhibition as measures of impulsivity in AD/HD: A supplement to the NIMH multimodal treatment study of AD/HD. *J Abnorm Child Psychol* 29:215–228.
- Sonuga-Barke EJ (2003): The dual pathway model of AD/HD: An elaboration of neuro-developmental characteristics. *Neurosci Biobehav Rev* 27:593–604.
- Sonuga-Barke EJ, Taylor E, Sembi S, Smith J (1992): Hyperactivity and delay aversion—I. The effect of delay on choice. *J Child Psychol Psychiatry* 33:387–398.
- Sonuga-Barke EJ, Bitsakou P, Thompson M (2010): Beyond the dual pathway model: Evidence for the dissociation of timing, inhibitory, and delay-related impairments in attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 49:345–355.
- Sowell ER, Thompson PM, Welcome SE, Henkenius AL, Toga AW, Peterson BS (2003): Cortical abnormalities in children and adolescents with attention-deficit hyperactivity disorder. *Lancet* 362:1699–1707.
- Strohle A, Stoy M, Wrase J, Schwarzer S, Schlagenhauf F, Huss M, Hein J, Nedderhuth A, Neumann B, Gregor A, Juckel G, Knutson B, Lehmkuhl U, Bauer M, Heinz A (2008): Reward anticipation and outcomes in adult males with attention-deficit/hyperactivity disorder. *Neuroimage* 39:966–972.
- Sturm V, Lenartz D, Koulousakis A, Treuer H, Herholz K, Klein JC, Klosterkötter J (2003): The nucleus accumbens: A target for deep brain stimulation in obsessive-compulsive- and anxiety-disorders. *J Chem Neuroanat* 26:293–299.
- Tamm L, Menon V, Reiss AL (2002): Maturation of brain function associated with response inhibition. *J Am Acad Child Adolesc Psychiatry* 41:1231–1238.
- Tamm L, Menon V, Reiss AL (2003): Abnormal prefrontal cortex function during response inhibition in Turner syndrome: Functional magnetic resonance imaging evidence. *Biol Psychiatry* 53:107–111.
- Tamm L, Menon V, Ringel J, Reiss AL (2004): Event-related fMRI evidence of frontotemporal involvement in aberrant response inhibition and task switching in attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 43:1430–1440.
- Tripp G, Wickens JR (2008): Research review: Dopamine transfer deficit: A neurobiological theory of altered reinforcement mechanisms in ADHD. *J Child Psychol Psychiatry* 49:691–704.
- Tucha L, Tucha O, Laufkotter R, Walitza S, Klein HE, Lange KW (2008): Neuropsychological assessment of attention in adults with different subtypes of attention-deficit/hyperactivity disorder. *J Neural Transm* 115:269–278.
- Volkow ND, Wang GJ, Kollins SH, Wigal TL, Newcorn JH, Telang F, Fowler JS, Zhu W, Logan J, Ma Y, Pradhan K, Wong C, Swanson JM (2009): Evaluating dopamine reward pathway in ADHD: Clinical implications. *JAMA* 302:1084–1091.
- Vollm BA, Richardson P, Stirling J, Elliott R, Dolan M, Chaudhry I, Del BC, McKie S, Anderson I, Deakin B (2004): Neurobiological substrates of antisocial and borderline personality disorder: Preliminary results of a functional fMRI study. *Crim Behav Ment Health* 14:39–54.
- Wacker J, Dillon DG, Pizzagalli DA (2009): The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: Integration of resting EEG, fMRI, and volumetric techniques. *Neuroimage* 46:327–337.
- Ward MF, Wender PH, Reimherr FW (1993): The Wender Utah rating scale: An aid in the retrospective diagnosis of childhood attention deficit hyperactivity disorder. *Am J Psychiatry* 150:885–890.
- Wechsler D (1977): *Wechsler Adult Intelligence Scale*, Vol. 3. San Antonio, TX, The Psychological Corporation.
- Wolfensberger SP, Veltman DJ, Hoogendijk WJ, De Ruiter MB, Boomsma DI, de Geus EJ (2008): The neural correlates of verbal encoding and retrieval in monozygotic twins at low or high risk for depression and anxiety. *Biol Psychol* 79:80–90.