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Janssen, T.W.P.

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CHAPTER 3

Neural correlates of response inhibition in children with attention-deficit/ hyperactivity disorder: a controlled version of the stop-signal task

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ABSTRACT

Objective: The stop-signal task has been used extensively to investigate the neural correlates of inhibition deficits in children with ADHD. However, previous findings of atypical brain activation during the stop-signal task in children with ADHD may be confounded with attentional processes, precluding strong conclusions on the nature of these deficits. In addition, there are recent concerns on the construct validity of the SSRT metric. The aim of this study was to control for confounding factors and improve the specificity of the stop-signal task to investigate inhibition mechanisms in children with ADHD. **Methods:** FMRI was used to measure inhibition related brain activation in 17 typically developing children (TD) and 21 children with ADHD, using a highly controlled version of the stop-signal task. Successful inhibition trials were contrasted with control trials that were comparable in frequency, visual presentation and absence of motor response. **Results:** We found reduced brain activation in children with ADHD in key inhibition areas, including the right inferior frontal gyrus/insula, and anterior cingulate/dorsal medial prefrontal cortex. **Conclusion:** Using a more stringent controlled design, this study replicated and specified previous findings of atypical brain activation in ADHD during motor response inhibition.

INTRODUCTION

Almost two decades ago, Barkley postulated an influential model on impaired response inhibition as the underlying deficit in attention-deficit/hyperactivity disorder (ADHD) (Barkley, 1997). According to that model, impaired response inhibition leads to deficits in other executive function (EF) domains and the phenotypic manifestation of ADHD. This model has led to an extended literature on EF in ADHD, with emphasis on inhibitory functioning. The stop-signal task (SST), which has been used extensively to investigate Barkley's model, requires participants to withhold a motor response to a frequently presented go signal when prompted by an infrequent and unpredictable stop signal (Logan, Cowan, & Davis, 1984; Logan & Cowan, 1984). The speed of the inhibition process appears to be slower in children with ADHD, as reflected in slower stop-signal reaction times (SSRT) (Oosterlaan, Logan, & Sergeant, 1998).

However, two more recent meta-analyses on the SST, utilizing an extended literature and including moderator variables, question the interpretation of slower SSRT in children with ADHD as reflecting poor inhibition (Alderson, Rapport, & Kofler, 2007; Lijffijt, Kenemans, Verbaten, & van Engeland, 2005). Instead, the authors conclude that differences in SSRT may be confounded by general slowing in mean reaction time (MRT) and increased reaction time variability (RTV), which is more in line with a general deficit in attentional or cognitive processing.

Neuroimaging studies using the SST in typically developing (TD) participants showed that successful stopping activates a brain network comprising the inferior frontal gyrus (IFG)/anterior insula, dorsal medial prefrontal cortex (dmPFC) including the pre-supplementary motor area (pre-SMA)/SMA and dorsal anterior cingulate cortex (ACC), and striatal and subthalamic nuclei (Swick, Ashley, & Turken, 2011). A recent meta-analysis (McCarthy, Skokauskas, & Frodl, 2014) of five SST studies in children with ADHD showed reduced activation in bilateral IFG/Ins, right medial frontal gyrus, and right superior and middle frontal gyri. Partially overlapping results were found in another meta-analysis (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013) of 15 studies using the SST or go-nogo (GNG) tasks, with reduced activation for ADHD in the right IFG/Ins, right SMA and ACC, right thalamus, left caudate and right occipital cortex. Contradicting results between the two meta-analyses may be explained by the inclusion of GNG task studies in Hart et al. (2013).

Although there is convincing evidence for atypical brain activation in ADHD during the SST, the interpretation of these findings is challenging. One major methodological concern for the SST is the confounding attentional capture effect of infrequent stop stimuli (Pauls et al., 2012; Sharp et al., 2010), which is not controlled with the conventional contrast between stop

and go conditions. Furthermore, several brain areas including the rIFG, which are activated during the SST, are also activated in oddball paradigms and are part of a right lateralized ventral attentional system (Corbetta, Kincade, & Shulman, 2002; Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010; Rubia, Hyde, Halari, Giampietro, & Smith, 2010). These findings suggest that typical SST activations may be confounded with attentional processes.

Particularly, the functional role of the rIFG is subject to debate, with some studies supporting a crucial role in detection of salient stimuli (Hampshire et al., 2010; Sharp et al., 2010), while other studies support a specific role in inhibition (Aron, Robbins, & Poldrack, 2004), and again other studies support both functions (Verbruggen, Aron, Stevens, & Chambers, 2010). This debate is particularly relevant for ADHD when considering the possibility that slower SSRT in ADHD may be explained by a deficit in attention (Alderson et al., 2007; Lijffijt et al., 2005) rather than an inhibition deficit. However, previous SST fMRI studies in ADHD have not controlled for attentional capture.

A few studies with the SST have attempted to control for attentional capture in healthy adult populations with different results. Sharp et al. (2010) added infrequent continue signals to the SST to control for attentional capture. Brain activation for the control and successful inhibition conditions overlapped in the rIFG, with only activation in the pre-SMA being uniquely associated with inhibition. Recent research however suggests that continue signals may engage alternative strategies, which could violate stop task assumptions (Bissett & Logan, 2014). In contrast, de Ruiter et al. (2012) found successful inhibition to be related to activation in both IFG and pre-SMA after controlling for attentional capture using a different control method.

The current study aimed to improve our understanding of inhibition deficits in children with ADHD by delineating inhibition-related brain activation during a SST that controls for the attentional capture effect of stop stimuli. Based on previous studies, we hypothesized that children with ADHD will show less activation in the dmPFC than TD children, and in the case of a specific inhibitory role for the rIFG in children, will show reduced activation in the rIFG as well. In accordance to Alderson et al. (2007) and Lijffijt et al. (2005), we expected that children with ADHD will perform worse than TD children, with evidence for inhibition problems (increased SSRT), but also for more general attentional problems (increased MRT, RTV, omission errors). Finally, additional analyses were performed to assess error-related brain activation during failed inhibition.

METHODS

Participants

Thirty-eight right-handed children aged between 8 and 13 years participated in this study (after final exclusion, see below), with 21 children in the ADHD group (19 males, 2 females), and 17 children in the TD group (13 males, 4 females), see Table I. Inclusion required an estimated full scale IQ≥70 measured with a short version of the Wechsler Intelligence Scale for Children (WISC-III; Wechsler, 1991), using the subtests Vocabulary, Arithmetic, Block Design and Picture Arrangement. Children were excluded if there was a known history of neurological conditions, presence of brain anomalies as assessed by a neuroradiologist (2 children with ADHD), or failure to meet basic task demands of at least 5 runs with >70% correct go trials (1 child with ADHD). Parents and children aged 12 years or older signed informed-consent. The study was conducted according to the Declaration of Helsinki, and approved by the ethics committee of the VU Medical Centre (Amsterdam, The Netherlands).

The ADHD group was recruited through outpatient mental health facilities in the Amsterdam area. All children obtained a clinical diagnosis of ADHD according to the DSM-IV (American Psychiatric Association 1994) as established by a child psychiatrist. ADHD diagnosis was confirmed with the parent version of the Diagnostic Interview Schedule for Children (DISC-IV; Shaffer et al., 2000), and by parent and teacher ratings on the Disruptive Behaviour Disorders Rating Scale (DBDRS; Pelham et al., 1992), which required scores above the 90th percentile for parents and teachers. According to DISC criteria, 19 children fulfilled ADHD combined subtype criteria and 2 children met ADHD inattentive subtype criteria. Exclusion criteria were comorbidity with other psychiatric disorders, except oppositional defiant disorder (as assessed with the DISC). Two children were medication naïve, and 19 children discontinued stimulant medication at least 48 hours before testing.

The TD group was recruited through local advertisement and in primary schools in the Amsterdam area. TD children were required to obtain normal scores on parent and teacher reported DBDRS (<90th percentile) and to be free of any psychiatric disorder.

Stimuli and task

The SST involved four trial types: go trials, stop trials and two types of trials that were used to control for confounding activation during successful and failed stop trials (see Figure 1). The go trials involved left or right pointing airplanes requiring a button press with the left or right index finger, respectively. Each trial started with a white fixation cross, centred on a black background

for 500 ms, followed by a 1500 ms go stimulus. Inter-trial-intervals varied randomly between 1000 ms and 5000 ms. In a randomly selected 16.6% of the trials, go stimuli were followed by a visual stop signal (a white cross) superimposed on the go stimulus, requiring the participants to withhold their response. At the start of the experimental session, stop-signal delay (SSD) was set to the average SSD obtained in the preceding training session, which took place outside the scanner. For the training and experimental sessions, the SSD between the go and stop stimuli was adapted trial-by-trial using an online tracking algorithm which increased or decreased the delay by 50 ms, depending on whether or not the previous stop trial resulted in successful inhibition (Logan, Schachar, & Tannock, 1997). This procedure yielded approximately 50% successful inhibitions (SI) and 50% failed inhibitions (FI). In control trials for SI (SI-C), which were randomly presented in 8.3% of the trials and as frequently as SI trials (half of 16.6% stop trials), the stop signal appeared first and was followed after the current SSD by the go stimulus. This trial type was designed to be analogous to SI trials in (1) stimulus complexity, controlling for differences in visual processing, (2) frequency, controlling for attentional capture, and (3) absence of motor response, to isolate neural activation specifically related to active response inhibition (Heslenfeld & Oosterlaan, 2003). In control trials for FI (FI-C), which were randomly presented in 8.3% of the trials and as frequent as FI trials, the stop signal appeared after a response had been made (in contrast to FI, where the stop signal preceded the response). The delay between the response and stop stimuli on FI-C trials varied concordantly with SSD. This trial type controlled for the same issues as SI-C while allowing a motor response, to obtain a more specific measure of error related neural processes (Heslenfeld & Oosterlaan, 2003). Note that all events within each trial occurred within several hundred milliseconds, such that the resulting fMRI responses will be sensitive to the processes initiated by the type of trial as such, rather than the order of the individual events.

Participants first practiced two runs outside the scanner, and subsequently, one practice run and eight experimental runs of 60 trials were administered in 30 minutes with trials presented in a pseudo-randomized order. Participants were instructed to respond both quickly and accurately to the go stimuli, and to refrain from responding when prompted with a stop signal. They were told that they would be unable to withhold their responses on all stop trials, and that they should not wait for the stop stimulus. Furthermore, they were instructed that some trials started with the stop stimulus and that these instances did not require a response, and that occasionally a stop sign followed their response on go trials.

fMRI image Acquisition

Images were acquired on a 1.5-T Siemens Sonata scanner (Siemens Medical Systems, Erlangen, Germany), equipped with a volume head coil. Stimuli were viewed through a mirror mounted on the head coil. Functional images were collected using a T2*-weighted echo-planar imaging (EPI) sequence scanning the whole brain with 20 5.0-mm slices (TR=2000 ms, TE=60 ms, FA=90°, 64x64 matrix, 3.0x3.0 mm in-plane resolution, gap 20%). Eight functional runs (115 volumes each) were collected. A 3-D anatomical scan was collected after the experimental session using a T1-weighted MP-Rage sequence (TR=2700 ms, TE=3.43 ms, TI=1000 ms, FA=7°, 256x160 matrix, 1.0x1.0 mm in-plane resolution, 160 1.25 mm slices).

fMRI data analysis

MRI data were analysed with Brainvoyager QX-2.3 software (Maastricht, the Netherlands). Preprocessing steps involved: exclusion of the first two volumes of each run from the analysis to allow longitudinal magnetization to arrive at a steady state; realignment of volumes to the third volume of each run with a rigid-body 3-D motion correction; slice scan time correction; 3-D spatial smoothing with a 6-mm fullwidth at half maximum (FWHM) Gaussian kernel; high-pass filtering (0.02Hz) to remove low frequencies; and low-pass filtering with a 3-s FWHM Gaussian kernel to remove high frequencies. Functional scans were coregistered to each individual anatomical scan, spatially normalized to Talairach space with the 9-parameter landmark method, and resampled at 3x3x3 mm resolution (Goebel, Esposito, & Formisano, 2006).

At the individual level, blood oxygen-level dependent (BOLD) responses of each voxel in each run were modelled with a general linear model (GLM) including five experimental regressors and seven nuisance regressors. The first five regressors accounted for successful inhibition (SI), successful inhibition control (SI-C), failed inhibition (FI), failed inhibition control (FI-C) and correct go trials. The last seven accounted for motion within each run with three translation and three rotation parameters in x, y, and z dimensions, and error trials that included erroneous responses other than failed inhibitions (i.e., commission and omission errors on go and control trials), which were modelled as regressors of no interest. The hemodynamic response to each event was modelled by convolving each regressor with a standard two-gamma HRF. Beta estimates were obtained for each regressor by fitting the convolved model to the voxel time series after correction for temporal autocorrelation (Goebel et al., 2006).

Eleven fMRI runs of 10 subjects were excluded due to failure to meet criteria of >70% correct go trials (1 run for ADHD) or a strategic change of solely attending to the go instructions

as reflected in a SSD of 0 ms (2 runs for one child with ADHD), or due to excessive movement during scanning with more than 3 mm translation in x, y, or z dimensions (6 runs for ADHD, 2 for TD).

At the group level, random effect second-level analyses were performed separately for the ADHD and TD groups, resulting in statistical parametric maps for SI versus SI-C (successful inhibition contrast), and FI versus FI-C (failed inhibition contrast). The uncorrected maps with a voxelwise threshold of $p<0.05$ were corrected for multiple comparisons using cluster-size thresholding by Monte Carlo simulations to obtain significant clusters at $p<0.05$ at the whole brain level (required cluster threshold=92 voxels). The resulting activation clusters from the corrected TD and ADHD single-group maps were then analysed as inhibition-related regions of interest (ROI) for group differences. For the ROI analyses, individual subject ROI beta weights were calculated and extracted in Brainvoyager and used as dependent variables in group comparisons.

Statistical analysis

Demographic and performance data were compared between groups with ANOVA. Motion during the scanning session was tested for group differences with multivariate ANOVA. Assumptions of the SST such as independence of go and stop processes (MRT>mean signal-respond time), and comparability of RT skew and RT slowing were assessed (Verbruggen, Chambers, & Logan, 2013). RT slowing was tested with generalized estimated equations (GEE).

The extracted individual subject ROI beta weights were statistically analysed with GLMs in SPSS (Version 20). The alpha-level was Bonferroni-adjusted for the number of clusters within each contrast.

Variables for analysis of the performance data were number of omission (no response to go stimulus) and commission (incorrect response) errors during go trials, mean reaction time (MRT) of correct go trials, percentage correct go trials (number of go trials/total number of errors), mean SSD, reaction time variability (coefficient of variation [CV]: standard deviation/MRT), and SSRT, which was computed by subtracting SSD from MRT (Logan, 1994). Spearman correlations were performed between ROI betas, DBDRS scales and task parameters. Only ROI betas of activation clusters that differed between groups were used for these analyses. Alpha was set at 0.05, two-tailed.

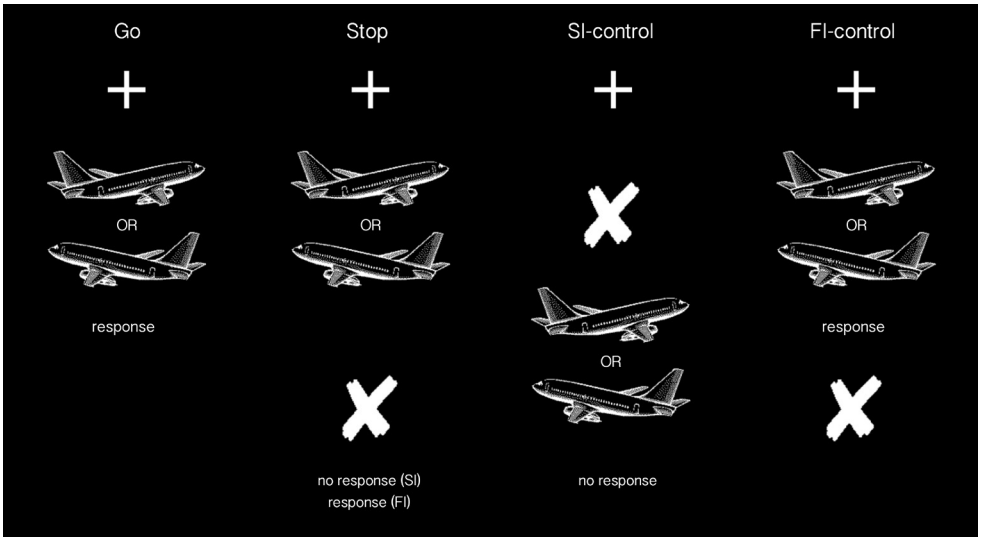

Figure 1. Trial types in controlled stop task
Note. SI=successful inhibition; FI=failed inhibition. Note that in the SI-control condition, the go stimulus (airplane) is not followed by a response.

RESULTS

Group characteristics and behavioural data

Table 1 summarizes the demographic and task performance data. Groups did not differ on age. There was a non-significant trend (p=0.061) for higher IQ in the TD group compared to the ADHD group. However, IQ did not correlate significantly with any of the outcome measures in this study (p-values>0.162). Mean go RT was slower than mean signal-respond RT, $F(1,36)=52.27$, $p<0.001$, no differences were found between groups in skewness of go RT distributions, $F(1,36)=0.32$, $p=0.58$, RT slowing, Wald $\chi^2(1)=2.07$, $p=0.15$, or percentage of successful inhibition, indicating the assumptions of the race model were met. Furthermore, groups did not differ significantly on number of runs on the SST. At last, the ADHD group showed slower SSRTs and made more omission errors than the TD group.

Multivariate ANOVA showed no significant differences between groups on translation or rotation parameter in x, y, or z dimensions, $F(6,31)=1.05$, $p=0.50$.

Table I. Group characteristics and task performance

	ADHD (*n*=21)		TD (*n*=17)		Between-group difference	
	M	*SD*	*M*	*SD*	*F*(1,36)	*p*
Demographic data						
Age (years)	10.63	1.11	10.28	1.21	0.82	ns
IQ	98.64	15.91	108.74	16.08	3.75	ns
Gender (M/F)	19/2	N/A	13/4	N/A	1.39[a]	ns
DBDRS parents						
Inattention	21.24	3.63	3.24	2.51	300.33	<0.001
Hyperactivity/ Impulsivity	19.00	7.38	3.11	2.25	73.09	<.001
DBDRS teacher						
Inattention	14.95	5.53	1.48	1.83	92.34	<0.001
Hyperactivity/ Impulsivity	13.38	4.97	2.37	3.11	63.37	<0.001
Stop-Signal Task						
Runs (number)	7.57	0.60	7.88	0.33	3.67	ns
Correct Stop (%)	48.18	3.02	49.59	1.48	3.10	ns
SSRT (ms)	295.82	56.26	236.74	33.64	14.50	0.001
MRT (ms)	530.89	113.77	486.68	97.36	1.61	ns
CV	0.25	0.05	0.21	0.06	3.12	ns
Omissions	7.10	6.88	3.29	3.82	4.14	0.049

Note. TD = typically developing; DBDRS = Disruptive Behavior Disorders Rating Scale; SSRT = stop-signal reaction time; MRT = mean reaction time on correct Go trials; CV = coefficient of variation; [a]$\chi^2(1)$

Brain activations during successful and failed inhibition

Brain activation for the successful inhibition and failed inhibition contrasts, for both groups separately, are shown in Figure 2 and Table 2.

Successful inhibition contrast. The successful inhibition contrast comparing SI and SI-C trials showed increased activation during SI trials in the TD group for the right IFG/insula, left insula, bilateral anterior cingulate cortex (ACC)/anterior medial frontal cortex and right medial/superior frontal cortex. In the ADHD group this contrast showed increased activation during SI

trials in the right insula and middle/superior frontal cortex, left insula and ACC.

Failed inhibition contrast. The failed inhibition contrast comparing FI and FI-C trials showed no activation in the TD group. In the ADHD group this contrast showed activation in bilateral premotor/primary motor areas, the ACC/dorsal medial frontal cortex and right middle/superior frontal cortex.

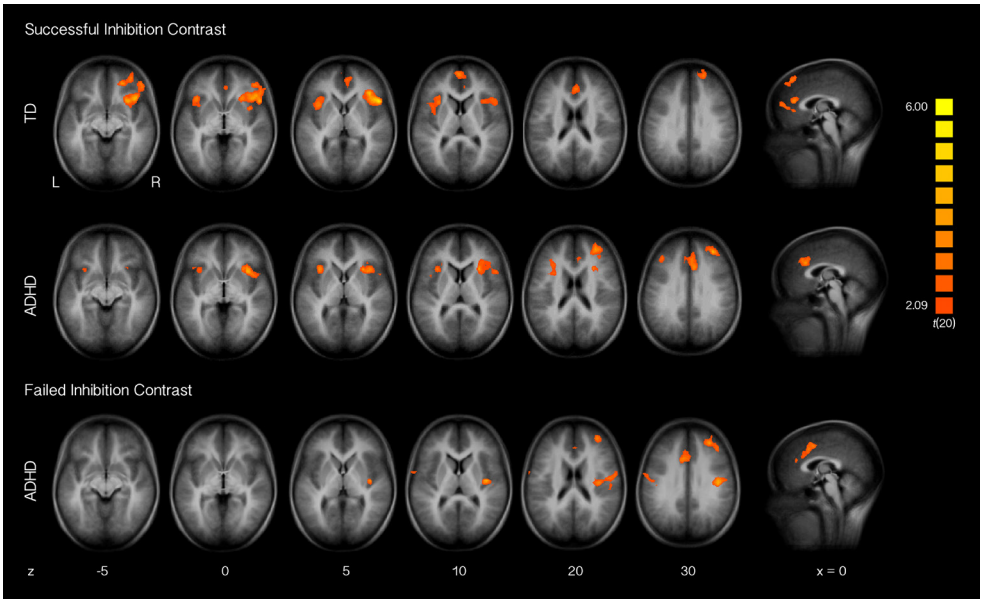

Figure 2. Statistical maps for the successful and failed inhibition contrasts for the TD and ADHD groups
Note. Significant activation clusters with a cluster-size corrected threshold of $p<0.05$ overlaid on the averaged Talairach-normalized image of all children. Note that the lower-bound in the TD group is $t(16) = 2.12$ for $p<0.05$; R = right hemisphere, L = left hemisphere; z = vertical Talairach coordinate; x = sagittal coordinate; t = t-statistic

Between-group comparisons

The within-group activation clusters were tested as inhibition-related regions of interest for group differences. P-values were Bonferroni-adjusted for the successful inhibition contrast (for TD clusters $p=0.05/4=0.0125$, for ADHD clusters $p=0.05/3=0.0167$) and failed inhibition contrast (for the ADHD clusters $p=0.05/4=0.0125$), based on the number of clusters per group. Results of the between-group analyses are shown in Table II.

Successful inhibition contrast. For the ROIs based on the TD group, the ADHD group activated the right IFG/insula and ACC/anterior medial frontal cortex to a lesser extend than the TD group. There was also a near-significant trend for reduced activation in the ADHD group in a more dorsally located dmPFC area including the right pre-SMA, extending to the right superior frontal cortex. No differences between groups were found for the ROIs based on the ADHD group.

Failed inhibition contrast. For the ROIs based on the ADHD group, the TD group showed less activation in bilateral premotor/primary motor areas compared to the ADHD group.

Sensitivity analysis. Analyses were repeated with only male subjects, showing the same pattern of results.

Correlations

A strong correlation was obtained between parent reported hyperactivity/impulsivity symptoms in the ADHD group and activation in the right motor cortex during FI, $r(19)=0.66$, $p=0.001$.

Table II. Activated brain regions for successful and failed inhibition contrasts, separately for TD and ADHD, and comparisons between groups

Area[a]	Side	Peak Voxel			Brodmann Area	Voxels		Between-group Difference[b]			
Successful Inhibition Contrast		x	y	z		*n*	*p*	*F*(1,36)	*p*	η^2	Direction
TD											
Inferior Frontal Cortex, Insula, Claustrum,	R	47	16	3	47,44,45,13	365	<0.001	9.03*	0.005	0.20	TD > ADHD
Insula, Claustrum	L	-34	10	3	13	107	0.016	0.33	ns		
Anterior Cingulate/Anterior Medial Frontal Cortex	L/R	5	34	15	32,24,10	100	0.028	8.34*	0.007	0.19	TD > ADHD
Medial/Superior Frontal Cortex	R	20	55	27	9,8,6	92	0.050	6.86†	0.013	0.16	TD > ADHD
ADHD											
Insula, Middle/Superior Frontal Cortex, Claustrum	R	32	40	30	13,9.10	330	<0.001	1.16	ns		
Insula, Claustrum	L	-31	16	6	13	130	0.005	3.46	ns		
Anterior Cingulate	L/R	5	19	33	32,24,9	117	0.010	2.05	ns		
Failed Inhibition Contrast											
ADHD											
Precentral Gyrus, Posterior Insula	R	38	-11	9	6,4,13	218	<0.001	8.34*	0.007	0.19	ADHD > TD
Anterior Cingulate/Dorsal Medial Frontal	L/R	5	13	38	32,24	175	<0.001	1,95	ns		
Precentral Gyrus, Postcentral Gyrus	L	-43	-17	33	6,4,3	115	0.007	7.48*	0.010	0.17	ADHD > TD
Middle/Superior Frontal Cortex	R	29	40	33	9,10	92	0.050	4.70	ns		

Note. [a]Significant activation clusters with a clustersize corrected threshold of $p<0.05$; R = right hemisphere, L = left hemisphere; peak voxel is the most significant voxel in Talairach space; *n* = number of voxels; [b]Univariate GLMs to test for group differences for each region of interest (ROI).
* = significant after Bonferroni-correction; † = near significant at a Bonferroni-adjusted alpha level of $p=0.0125$, with $p=0.0128$

DISCUSSION

The present study aimed to advance the understanding of inhibition deficits in children with ADHD, by isolating inhibition-related brain activation in a highly controlled SST. In contrast to previous studies using the SST, our task controls for the confounding effects of attentional capture, visual presentation differences, and motor responses. As hypothesized, children with ADHD had a slower inhibition process (increased SSRT) and made more omission errors. No evidence was found for increased MRT and RTV. Both the TD and ADHD groups activated bilateral IFG/insular regions and the ACC. As expected, children with ADHD activated the rIFG/insula and dmPFC less than TD children during successful inhibition.

The imaging results of this study are largely in line with the meta-analysis of McCarthy et al. (2014) and Hart et al. (2013), showing reduced activation in rIFG/insula and dmPFC areas. The rIFG is part of a putative inhibition network, connected via a direct pathway with the subthalamic nucleus (STN), both of which are connected with the pre-SMA (Aron, 2007). Aron et al. (2007) propose that the rIFG implements inhibition at a neural level by activating the STN, which activates the globus pallidus, resulting in thalamo-motorcortical inhibition. The pre-SMA could have a conflict monitoring function or implement neural inhibition directly via the STN. Our results showed reduced activation in key areas of this inhibition network in ADHD, including the rIFG/insula, ACC and pre-SMA. The current findings support an inhibition-related dysfunction in children with ADHD.

Performance data in our study are also consistent with the idea of an inhibition-dysfunction in ADHD. SSRT differed significantly between groups, with the ADHD group having slower SSRTs than the TD group. Both SSD and MRT did not significantly differentiate groups. However, it cannot be ruled out that the SSRT difference between groups is partially driven by a difference in MRT as was suggested by Alderson and colleagues (Alderson et al., 2007).

Despite clear evidence for atypical brain activation in children with ADHD during the SST, previous neuroimaging studies either showed no performance differences between subjects with ADHD and controls (Cubillo et al., 2014; Pliszka et al., 2006; Rubia, Cubillo, et al., 2010b), or found evidence for attention related problems in ADHD in increased RTV (Rubia et al., 2008; Rubia, Halari, Mohammad, Taylor, & Brammer, 2011; Rubia, Smith, Brammer, Toone, & Taylor, 2005), or higher rates of omission errors (Rubia et al., 2005). Only two studies found lower rates of probability of inhibition (Rubia, 2001; Rubia et al., 1999), but no SSRT differences. These behavioural findings challenge the interpretation of the accompanying neuroimaging results.

Another important observation in this study is the role of anterior insular cortex during

successful inhibition. Swick et al. (2011) emphasized in their meta-analysis the unexpected greater prominence of insular activation compared to the IFG activation during GNG and stop tasks. They suggested two possible explanations. First, some studies interpret activation foci in the insula as IFG activations due to localisation error, or second, spatial smoothing methods can blur spatially distinct patterns and lead to errors in localisation of brain activation. The insula is described as a highly integrative area, and is found in a wide range of cognitive tasks (Kurth, Zilles, Fox, Laird, & Eickhoff, 2010). Singer et al. (2009) proposed that the insula plays an important role in the signalling of uncertainty. Although our SST controlled for attentional capture, SI trials and SI-C trials were somewhat different in respect to uncertainty. SI trials started with a go signal, for which the child was uncertain whether or not a stop-signal would occur afterwards. In contrast, SI-C were as frequently and randomly presented as SI trials, but started with a stop signal, with no uncertainty about immediate subsequent events. In conclusion, the bilateral insular activation in our study might also be related to uncertainty, as well as inhibition.

Error related brain activation in the SST was not as expected. For the TD group no activity was found, whereas for the ADHD group activation was found in a typical error/conflict monitoring area, the ACC (Shenhav, Botvinick, & Cohen, 2013), and bilateral motor areas. The absence of activation in the TD group could be due to a differential behavioural response to the control condition as compared to the ADHD group. The control condition was equal to a normal go trial; however, the manual response was followed by a stop-signal to control for confounding visual input. Possibly, TD children interpreted the appearance of the stop-signal, despite the task instructions, as an error, removing (or reducing) the resulting activation from the failed inhibition condition. The ADHD group also activated right motor areas during FI, which correlated with hyperactivity/impulsivity as reported by parents. Possibly, this finding might be explained by a lower frustration threshold in ADHD (Mick, Spencer, Wozniak, & Biederman, 2005), accompanied by more motor restlessness in response to errors in ADHD.

Some limitations of this study should be noted. First, most children in the ADHD group were on stimulant medication. Although medication use was discontinued before testing, long-term effects of chronic treatment with MPH on brain functioning have been reported, with one study showing normalization (Bush et al., 2008), while others found MPH to be insufficient to normalize neurofunctional deficits (Konrad, Neufang, Fink, & Herpertz-Dahlmann, 2007; Schweitzer et al., 2004). For the SST in particular, activation differences between children with ADHD and TD in the right superior frontal gyrus were larger in treatment naive children in the

meta-study of McCarthy et al. (2014). In the current study, we found a near significant effect for reduced activation in the right medial/superior frontal gyrus in ADHD during successful inhibition, which did not survive Bonferroni-correction. It cannot be ruled out that chronic stimulant use diminished group differences in this brain area. Furthermore, acute medication withdrawal effects may have affected our results. The meta-study by McCarthy et al. (2014) found an effect of medication washout-length on brain activation. More specifically, shorter washout periods meant fewer activation differences compared to controls in the left medial frontal gyrus, and longer washout periods meant more activation differences compared to controls in the right precuneus. These results suggest that acute effects of treatment cessation, similarly to long-term medication effects, are associated with normalized brain activity. Consequently, brain activation differences in our study may have been reduced. However, our finding of reduced activation in rIFG is in line with fMRI studies in medication-naïve boys with ADHD (Rubia et al., 2005; Rubia, Cubillo, et al., 2010a), increasing the confidence in our findings.

Another limitation is that the control conditions may have induced inhibition-related activation that in turn would have diminished differences obtained in our successful and failed inhibition contrasts. Although task instructions clearly stated that control trials did not require a response, their infrequency compared to go trials could have triggered partial inhibition, comparable to a nogo trial in a GNG task. The successful inhibition contrast showed activation in key motor inhibition areas, but effects in other brain areas, especially basal ganglia nuclei such as the striatum (Vink et al., 2014; Zandbelt & Vink, 2010), could have been diminished; although this could also be the result of the cluster-size thresholding method, which may be less likely to show smaller activation areas. Future study designs of the stop task could use a neutral stimulus in the control condition to reduce the go/no-go inhibition effect. A second limitation may be that only SI trials involve a fast redirection of attention from go to stop instructions (cognitive set-shifting), in contrast to control trials (SI-C). This may have contributed to differences between SI and SI-C trials even though both types of trials were equated for stimulus-related, response-related, and probability-related processes (i.e. attentional capture).

In conclusion, this study confirmed hypoactivation in key inhibition areas in children with ADHD, while controlling for the confounding effects of attentional capture, visual presentation differences, and motor response. Furthermore, these findings were complemented by evidence for inhibitory control problems at the behavioural level. To our knowledge, this is the first study in children with ADHD that incorporates stringent control conditions in the SST in order to isolate inhibition-related brain activation.

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