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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

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. 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. 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. Using a more stringent controlled design, this study replicated and specified previous findings of atypical brain activation in ADHD during motor response inhibition.

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1. 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 task, 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 and Cowan, 1984; Logan et al., 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 et al., 1998).

However, two more recent meta-analyses on the stop task, utilizing an extended literature and including moderator variables, question the interpretation of slower SSRT in children with ADHD as reflecting poor inhibition (Lijffijt et al., 2005; Alderson et al., 2007). 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 stop task 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 et al., 2011). A recent meta-analysis (McCarthy et al., 2014) of five stop task 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 et al., 2013) of 15 studies using the stop task 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).

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Although there is convincing evidence for atypical brain activation in ADHD during the stop task, the interpretation of these findings is challenging. One major methodological concern for the stop task is the confounding attentional capture effect of infrequent stop stimuli (Sharp et al., 2010; Pauls et al., 2012), 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 stop task, are also activated in oddball paradigms and are part of a right lateralized ventral attentional system (Corbetta et al., 2002; Hampshire et al., 2010; Rubia et al., 2010c). These findings suggest that typical stop task 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 et al., 2004), and again other studies supporting both functions (Verbruggen et al., 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 (Lijffijt et al., 2005; Alderson et al., 2007) rather than an inhibition deficit. However, previous stop task fMRI studies in ADHD have not controlled for attentional capture.

A few studies with the stop task have attempted to control for attentional capture in healthy adult populations with different results. Sharp et al. (2010) added infrequent continue signals to the stop task 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 and 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 stop task 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.

Table 1
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	< 0.001
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 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
MRT (ms)	530.89	113.77	486.68	97.36	1.61	ns
CV RT	0.25	0.05	0.21	0.06	3.12	ns
SSD (ms)	235.07	92.68	249.94	87.08	0.26	ns
SSRT (ms)	295.82	56.26	236.74	33.64	14.50	0.001
Commission Errors	10.29	6.69	7.88	5.96	1.34	ns
Omission Errors	7.10	6.88	3.29	3.82	4.14	0.049

Note. DBDRS = Disruptive Behavior Disorders Rating Scale; MRT = mean reaction time on correct Go trials; CV = coefficient of variation; SSD = stop-signal delay; SSRT = stop signal reaction time.

[a] $\chi 2(1)$

2. Methods

2.1. 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 1. 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 Behavior 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 h 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.

2.2. Stimuli and task

The stop task 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 Fig. 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

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