Attention for Inhibition

Janssen, T.W.P.

2016

document version
Publisher's PDF, also known as Version of record

CHAPTER 2

Alterations in the ventral attention network during the stop-signal task in children with attention-deficit/hyperactivity disorder: an ERP source imaging study

This chapter has been published as:

Janssen, T. W. P., Heslenfeld, D. J., van Mourik, R., Geladé, K., Maras, A., & Oosterlaan, J. (2015). Alterations in the Ventral Attention Network During the Stop-Signal Task in Children With ADHD: An Event-Related Potential Source Imaging Study. *Journal of Attention Disorders*

ABSTRACT

Objective: Deficits in response inhibition figure prominently in models of ADHD; however, attentional deficiencies may better explain previous findings of impaired response inhibition in ADHD. We tested this hypothesis at the neurophysiological level. **Methods:** Dense array ERPs were obtained for 46 children with ADHD and 51 controls using the stop-signal task. Early and late components were compared between groups. N2 and P3 components were localized with LAURA distributed linear inverse solution. **Results:** A success-related N1 modulation was only apparent in the ADHD group. N2 and P3 amplitudes were reduced in ADHD. During the successful inhibition N2, the ADHD group showed reduced activation in right inferior frontal gyrus (rIFG), supplementary motor area (SMA) and right temporoparietal junction (rTPJ), and during failed inhibition in the rIFG. During the successful inhibition P3, reduced activation was found in anterior cingulate cortex (ACC) and SMA. **Conclusion:** Impairments in the ventral attention network contribute to the psychopathology of ADHD and challenge the dominant view that ADHD is underpinned by impaired inhibitory control.

INTRODUCTION

Deficits in response inhibition are seen as one of the core problems in ADHD and figure prominently in theoretical models of the disorder (Barkley, 1997; Sonuga-Barke, Bitsakou, & Thompson, 2010). Empirical support for these models originates for an important part from the stop-signal task (SST) (Logan, Cowan, & Davis, 1984; Logan & Cowan, 1984). Although a majority of studies found evidence for a slower inhibition process in ADHD (Oosterlaan, Logan, & Sergeant, 1998), as reflected in slower stop-signal reaction times (SSRT), more recent meta-analyses suggest that the calculation of SSRT is disproportinionally influenced by slower reaction times to go stimuli in the ADHD group (Alderson, Rapport, & Kofler, 2007; Lijffijt, Kenemans, Verbaten, & van Engeland, 2005). Attentional deficiencies may therefore better explain previous findings of impaired response inhibition.

Moreover, imaging studies point to potential confounds in the SST that challenge findings of functional abnormalities in typical inhibition-related brain areas in ADHD. One major methodological concern is the attentional capture effect of infrequent stop stimuli (Pauls et al., 2012; Sharp et al., 2010), which in the same way as oddball stimuli, could induce activation in a ventral attention network important for target detection/saliency that partly overlaps with inhibition areas such as the right inferior frontal gyrus (rIFG) (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010). This raises doubt on the interpretation of well documented fMRI findings of reduced activation in rIFG/insula, supplementary motor area (SMA) and anterior cingulate cortex (ACC) in children with ADHD during SST (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013).

Event-related potential (ERP) findings of early processing alterations in ADHD during the SST further complicate the picture. Although the exploration of early exogenous ERP components is generally not the main focus of SST studies in ADHD, there are at least some studies suggesting altered sensory registration as reflected in reduced P1 amplitude (Shen, Tsai, & Duann, 2011), increased N1 amplitude (Dimoska, Johnstone, Barry, & Clarke, 2003; Johnstone, Barry, & Clarke, 2007) or increased as well as decreased P2 amplitudes (Dimoska et al., 2003; Senderecka, Grabowska, Szewczyk, Gerc, & Chmylak, 2012), although evidence is inconsistent. This inconsistency could be attributable to ineffective correction or the lack of correction of ERPs elicited by preceding go stimuli that distort stop ERPs, especially for early components such as N1 and P2 (Woldorff, 1993). If, indeed, problems in early sensory registration in ADHD exist, then these should be considered when interpreting findings of subsequent processing stages in ADHD.

Late endogenous components in the SST such as N2 and P3 have been studied more extensively and numerous studies have consistently shown reduced amplitudes in children with ADHD (Johnstone et al., 2007; Liotti et al., 2007; Liotti, Pliszka, Higgins, Perez, & Semrud-Clikeman, 2010; Pliszka et al., 2007). Liotti and Pliszka reported in multiple studies that the reduction in N2 amplitude is most pronounced at the right frontal scalp and that only typically developing (TD) children showed a success-related modulation of the right frontal N2 (Liotti et al., 2010; Pliszka et al., 2007; Pliszka, Liotti, & Woldorff, 2000a). Although both N2 and P3 have been associated with inhibition (Ramautar, Kok, & Ridderinkhof, 2004; van Boxtel, van der Molen, Jennings, & Brunia, 2001), there is still much debate about their functional significance. The N2 may signal conflict (Enriquez-Geppert, Konrad, Pantev, & Huster, 2010) and the P3 might reflect monitoring of the outcome of inhibition (Liotti, Pliszka, Perez, Kothmann, & Woldorff, 2005). Source localization studies of the N2 show inconsistent findings, with evidence for rIFG involvement (Lavric, Pizzagalli, & Forstmeier, 2004), associated with inhibition, but also ACC involvement (Nieuwenhuis, Yeung, van den Wildenberg, & Ridderinkhof, 2003), typically implicated in cognitive control functions such as conflict monitoring, or both (Bokura, Yamaguchi, & Kobayashi, 2001). The P3 has been localized in the ACC (Crottaz-Herbette & Menon, 2006), suggesting a role in cognitive control as well.

The discussed methodological concerns emphasize the need for a more comprehensive examination of the SST in ADHD. Therefore, the aims of the current study were twofold: (1) to assess the possible influence of early processing deficits in ADHD during the SST, and (2) to anatomically localize altered ERP components to gain both temporal and spatial insights in the involved neural networks. To aid these goals we employed the 'adjacent response filter method (ADJAR)' (Woldorff, 1993), which is effective in removing the overlap of preceding go ERPs (see Bekker et al. (2005) for a discussion and demonstration of ADJAR for the SST). Furthermore, individual distributed source localization of differentiating components was implemented. One of the main advantages over equivalent current dipole methods is that it is less prone to operator bias, and that is can handle multiple spatially extended sources (Pizagalli, 2007).

For the ADHD group we expected altered early N1/P2 responses and reduced N2 and P3 components. Based on ERP source imaging studies of N2 and P3 components and fMRI findings in ADHD, we expected the involvement of several altered brain networks associated with inhibition, attention and cognitive control. More specifically, we hypothesized reduced source activity during the N2 in rIFG and/or ACC, and during the P3 in ACC.

METHODS

Participants

Complete data were available for ninety-seven children in the age range 7 to 14 years with 46 children in the ADHD group (37 males, 9 females) and 51 children in the TD group (37 males, 14 females), see Table I. Inclusion required an estimated full scale IQ > 80, measured with a short version of the Wechsler Intelligence Scale for Children (WISC-III; Wechsler, 1991), using subtests Vocabulary, Arithmetic, Block Design and Picture Arrangement. Children were excluded if there was a known history of neurological conditions.

The ADHD group was recruited through mental health outpatient facilities in the West of the Netherlands. All children obtained a clinical diagnosis of ADHD combined type 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, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000), and by parent and teacher ratings on the Disruptive Behaviour Disorders Rating Scale (DBDRS; Pelham, Gnagy, Greenslade, & Milich, 1992), which required at least one of the scores on the Inattention or Hyperactivity/Impulsivity scales to be in the clinical (>90th percentile) range for both informants. Seventy-six per cent of children were naïve for stimulant medication and the remaining children discontinued use of stimulants at least 4 weeks before testing. Children with a clinical DSM-IV diagnosis of autism spectrum disorder were excluded.

The TD group was recruited through three primary schools and a sports club in the same recruitment area as the ADHD group. Control children were required to obtain normal scores on the DBDRS (<90th percentile) for both informants and to be free of any psychiatric disorder.

Procedure

The current study sample partly overlaps with a sample that later participated in a randomized controlled trial on the effects of neurofeedback, methylphenidate and physical activity as treatments for ADHD (trial number: NCT01363544). The study was conducted according to the Declaration of Helsinki, and approved by the ethics committee of the VU Medical Centre (Amsterdam, The Netherlands). Parents and children aged 12 years or older signed informed-consent.

Behavioural assessment

Symptom scales of Inattention and Hyperactivity/Impulsivity from parent and teacher reports

on the Strengths and Weaknesses of ADHD symptoms and Normal behaviour scale (SWAN; Swanson, Schuck, Mann, & Carlson, 2006) were used for correlational analyses with the primary outcome measures.

Stimuli and Task

The SST involved two types of stimuli: go stimuli and stop stimuli. Go stimuli were left or right pointing airplanes requiring either a left or right button response. Each trial started with a black fixation cross, centred on a white background for 500ms, followed by a go stimulus for 1250ms and a blank screen for 650ms. Inter-trial-intervals varied randomly between 0, 50, 100, 150 and 200ms. In a randomly selected 25% of the trials, go stimuli were followed by a visual stop signal (traffic stop sign) superimposed on the go stimulus, requiring the participants to withhold their response. The delay between the go and stop signal (stop-signal delay; SSD) varied trial-by-trial using a tracking algorithm which increased or decreased the delay with 50ms, depending on whether or not the previous stop trial resulted in successful inhibition. This procedure yielded approximately 50% successful inhibitions (SI) and 50% failed inhibitions (FI).

Two practice blocks (one containing 12 go trials and another containing 20 mixed go and stop trials) and 6 experimental blocks of 100 trials were administered in 25 minutes with the trials presented in a fixed randomized order. Participants were instructed to respond both quickly and accurately to the go stimuli and withhold their response when a stop signal was presented. 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 sign. The recording was interrupted by two short breaks of one minute. Performance was monitored online in order to check the participant's co-operation and protocol adherence, and if needed, additional standardized instructions were given during the one-minute breaks.

Variables for analysis of the performance data were number of omission (no response to go stimulus), mean reaction time (MRT) of correct go trials, reaction time variability (coefficient of variation [CV]: standard deviation/MRT), and SSRT, which was computed by subtracting mean SSD from MRT (Logan, 1994).

Electrophysiological recordings

Continuous electroencephalogram (EEG) was recorded at 512Hz using the ActiveTwo Biosemi system and ActiView software (Biosemi, Amsterdam, The Netherlands) from 128 scalp electrodes according to the ABC labelling system, referenced to the active common mode and

grounded to the passive driven right leg, which functions as a feedback loop to drive average potentials across electrodes to the amplifier zero. The electro-oculogram (EOG) was obtained using two electrodes at the external canthi, and two electrodes at infra- and supra-orbital sides. Reference electrodes were placed at both mastoids.

Off-line analysis was performed with Brain Vision Analyzer 2 software (Brain Products, Gilching, Germany). A band-pass filter of 0.1-30Hz at 24 dB/oct and a 50-Hz notch filter were applied, and scalp electrodes were re-referenced to the average of the mastoids. Ocular artefacts were estimated and corrected with a semi-automatic independent component analysis (ICA) using a restricted infomax algorithm (Jung et al., 2000), and automatic artefact rejection was applied to segments based on the following criteria: maximum allowed voltage step of 50μV/ms, maximal peak-to-peak amplitude difference of ±150μV, and minimal low activity of 0.50μV for 100ms intervals. Broken electrodes were interpolated with the spherical splines method (Perrin, Pernier, Bertrand, & Echallier, 1989).

Correct go trials were segmented from 700ms pre-stimulus to 1700ms post-stimulus and baseline-corrected for the interval -700 to -500ms; this interval precedes the fixation cross during the presentation of a blank screen between trials. Both SI and FI trials were first segmented at the preceding go stimulus using an equal interval and baseline correction as previously described. Due to the adjacency between go and stop stimuli, go and stop responses in the EEG overlap. We corrected for this with ADJAR (Woldorff, 1993), which filters out overlap of previous go responses. After this correction, trials were segmented from -100ms to 800ms relative to the stop stimulus. Subsequently, a 100ms pre-stimulus baseline was applied and averages were obtained for SI and FI.

Grand average ERPs, scalp topographies and difference waves for each trail type were inspected to define analysis windows for N1(105-155ms), P2(175-225ms), N2(240-290ms), and P3(320-420ms). Although a late positive wave (LPW) was apparent around 650ms, this component is beyond the scope of the current article. Mean voltage amplitudes were used for statistical analyses.

LAURA source estimation

Sources underlying differentiating ERP components between groups were estimated for each time-window using the LAURA distributed linear inverse solution method (Grave de Peralta Menendez, Gonzalez Andino, Lantz, Michel, & Landis, 2001; Grave de Peralta Menendez, Murray, Michel, Martuzzi, & Gonzalez Andino, 2004; Michel et al., 2004). The analysis was performed

using the Cartool software by Denis Brunet (brainmapping.unige.ch/cartool). Only main group effects were examined.

LAURA is a regularization method that incorporates biophysical laws to obtain the optimal solution that fulfills both the observed data and bio-electromagnetic constraints. In this approach, the relationship between brain activity at one point and its neighbors is expressed in terms of local autoregressive estimator with coefficients depending upon a power of the distance from the point (Grave de Peralta Menendez et al., 2004). Cartool software uses the L-curve method to find the optimal regularization parameter for a given data file (Hansen, 1992). We used the Locally Spherical Model with Anatomical Constraints (LSMAC) as lead field model, which has been shown to perform as well as more computationally intensive models like the Boundary Element Model (BEM) (Birot et al., 2014). Inverse solutions were calculated for each participant separately on a realistic head model that included 5004 equally distributed nodes within the gray matter of the Montreal Neurological Institute (MNI) transformed NIHPD pediatric brain atlas based on 7.5-13.5 years old children (Fonov et al., 2011). The dependent variable that was used for statistical evaluation was the norm of the vector (intensity) of each node, which is the positive length or size of each vector.

The stability and reliability of LAURA and other distributed inverse solution methods have been validated by direct comparisons with intracranial recordings, lesion studies and other imaging methods (Pascual-Marqui, Sekihara, Brandeis, & Michel, 2009).

Statistics

Demographic and performance data were compared between groups using General Linear Model (GLM) ANOVA in SPSS 20 (Corp IBM, 2011). Alpha was set at 0.05, two-tailed. To explore the relation between brain responses, cognition and ADHD symptoms, Pearson correlations were computed between LAURA activations and SSRT, MRT, CV, omissions and SWAN symptom scales. Correlations of $p<.01$ were considered significant, and $p>.01$ and $p<.05$ as trend. Non-significant correlations were not reported. Assumptions of the SST such as independence of go and stop processes (MRT go trials>MRT FI trials), comparability of RT skew and RT slowing were assessed, see Verbruggen, Chambers, & Logan (2013) for a discussion. To account for within-subject correlation of responses, RT slowing was tested with generalized estimated equations (GEE). IQ was not entered as covariate in any of the analyses, as lower IQs are associated with ADHD (Frazier, Demaree, & Youngstrom, 2004), which violates assumptions of ANCOVA (Dennis et al., 2009).

For the N1, P2, and P3 analyses, repeated-measures GLM multivariate analysis of variance (MANOVAs) were performed with Group as between-subject factor (TD, ADHD) and with both Condition (SI, FI) and Location (Fz, Cz, Pz) as within-subject factors. To specifically test for right frontal dominance in N2 group differences, the analysis for N2 distinguished four averaged regions of interest (ROIs): left frontal (LF; C27, D4, D7), left parietal (LP; D17, D26, A7), right frontal (RF; C14, C4, C7) and right parietal (RP; B19, B16, B4). Findings involving group were further explored with Bonferroni-corrected post-hoc tests if necessary. When appropriate, conditions or locations were averaged for further post-hoc analysis.

For the LAURA estimations, group differences were tested with unpaired t-tests for each node. P-values were Bonferroni-corrected based on the number of electrodes, with p=.05/128=.0004 (Grave de Peralta Menendez et al., 2004). Coordinates were converted from MNI to Talairach space with the icbm2tal algorithm (Lancaster et al., 2007) using GingerALE software (Laird et al., 2005). Individual ROIs were computed for brain regions that differed significantly between groups by averaging the solution points to obtain correlations with performance measures.

RESULTS

Group characteristics and behavioural data

Table I summarizes the group characteristics and task performance data. Groups did not differ on age and gender. As expected, IQ was lower in the ADHD group. MRT go trials was slower than MRT FI trials, $F(1,95)=303.54$, $p<.001$, no differences were found between groups in skewness of go RT distributions, $F(1,95)=2.58$, $p=.111$, RT slowing, Wald $\chi^2(1)=-.439$, $p=.51$, or percentage of successful inhibition, $F(1,95)=0.01$, $p=.754$, indicating SST assumptions were met. Groups did not differ on SSRT. However, the ADHD group showed increased MRT and CV and made more omission errors than the TD group.

Number of artefact-free segments did not differ between groups for go trials (mean=299), $F(1,95)=2.61$, $p=.110$, SI trials (mean=66), $F(1,95)=1.48$, $p=.226$, and FI trials (mean=53), $F(1,95)=2.5$, $p=.114$, and there were no significant group differences in number of interpolations (mean=1.5), $F(1,95)=3.01$, $p=.086$).

ERP results

Mean amplitudes of the ERP components for each location, condition and group, and MANOVA

Table I. Group characteristics and task performance

	ADHD (*n*=46)		TD (*n*=51)		Between-group difference	
	M	*SD*	*M*	*SD*	*F*(1,95)	*p*
Demographic data						
Age (years)	9.71	1.97	9.88	1.21	0.29	ns
IQ	99.76	12.37	110.56	14.40	15.54	<.001
Gender (M/F)	37/9	N/A	37/14	N/A	0.83[a]	ns
DBDRS parents						
Inattention	17.35	5.20	3.69	3.40	239.11	<.001
Hyperactivity/ Impulsivity	17.07	4.87	3.12	2.82	305.29	<.001
DBDRS teacher						
Inattention	16.54	5.53	2.27	3.61	231.18	<.001
Hyperactivity/ Impulsivity	16.48	6.66	1.59	2.64	217.53	<.001
Stop-Signal Task						
SSRT (ms)	254.57	80.02	250.04	51.26	0.11	ns
MRT (ms)	645.25	103.96	568.35	101.38	13.58	<.001
CV	0.28	0.04	0.26	0.05	8.04	<.01
Omissions	16.20	13.03	7.47	7.08	17.24	<.001

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]$\chi^2(1)$

results are shown in Table II. Waveforms are shown in Figure 1.

N1 (105-155 ms). The three-way interaction between Condition, Location and Group was significant. Post-hoc tests revealed that only for the ADHD group, Condition and Location interacted significantly, $F(2,44)=6.15$, $p=.004$, $\eta_p^2=.22$, with only for Cz a significant larger N1 amplitude for SI than FI, $F(1,45)=5.45$, $p=.024$, $\eta_p^2=.11$. The main effect of Location indicated that amplitudes were larger at Fz compared to Cz and Pz.

P2 (175-225 ms). No differences were found between groups. Condition and Location interacted significantly. This interaction reflected larger P2 amplitude at Pz for SI than FI.

N2 (240-290 ms). Main effects were found for Condition, Location and Group. The main

effect of Group indicated that N2 amplitudes were smaller for the ADHD group than the TD group, mean difference=-3.57, 95%CI[-5.71,-1.43]. The main effect for Condition indicated that FI trials showed greater N2 amplitude than SI trials. The Location effect revealed that N2 amplitudes were maximal at right hemispheric parietal sites.

P3 (320-420 ms). Condition and group interacted. Post-hoc analysis revealed a trend for a group difference only for SI trials, $F(1,95)=3.77$, $p=.055$, $\eta_p^2=.04$, with smaller P3 amplitudes for the ADHD group, mean difference=3.06, 95%CI[-0.07,6.19]. The main effect of Condition indicated that P3 amplitudes were larger for SI than FI trials, whereas the main effect of Location revealed larger P3 amplitudes at Pz compared to Cz and Fz.

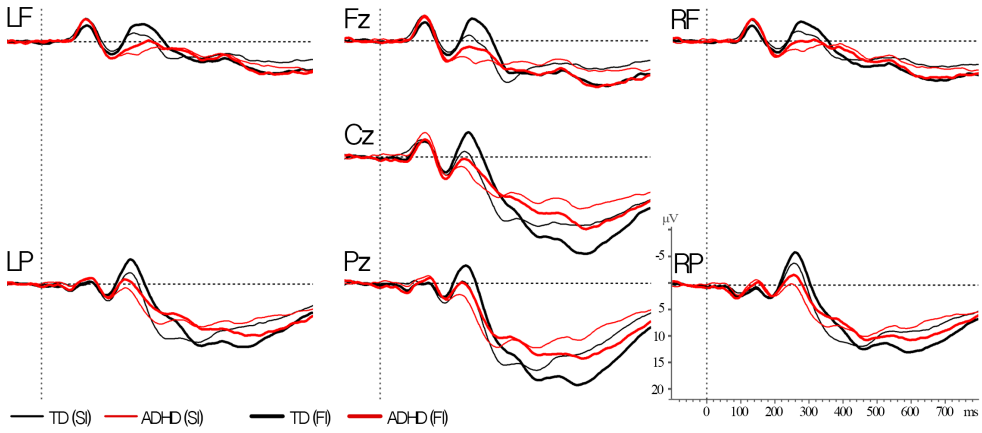

Figure 1. Grand average ERPs of the ADHD and TD groups on the stop-signal task

Note. Grand average ERPs for the ADHD and TD groups, for SI and FI for midline electrodes (Fz, Cz, Pz) and regions of interest: LF = left frontal, RF = right frontal, LP = left parietal, RP = right parietal. ERP = event-related potential; TD = typically developing; SI = successful inhibition; FI = failed inhibition; µV = microvolt, ms = millisecond.

LAURA source estimation results

Given the ERP findings of reduced N2 amplitudes during SI and FI, and reduced P3 amplitude during SI in ADHD, these analysis windows were used for LAURA source estimation. The N1 three-way interaction was not suitable for examination with LAURA, which only allows testing of main group effects. Figure 2 shows the statistical parametric maps of the group comparisons. For N2 during SI, the ADHD group showed reduced activation in right inferior frontal gyrus (rIFG)

and insula (Brodmann areas [BA] 44 and 13) extending into BA6, right temporoparietal junction (rTPJ; BA 40) and rostral medial frontal cortex (BA 6), including the supplementary motor area (SMA). See Figure 3 for a lateral view. During FI, the ADHD group showed reduced activation in the rIFG (BA44) for N2. Analyses for the subsequent P3 during SI showed reduced activation in children with ADHD compared to TD children in medial frontal areas, including the anterior cingulate cortex (ACC, BA 32, 24), and SMA (BA 6).

Correlations

Differentiating sources between groups during N2 and P3 were averaged for each child and correlated with performance measures and SWAN symptom scales.

Successful Inhibition. For N2 sources, the TD group showed a trend for a negative correlation between rIFG activation and SSRT, $r(49)=-.33$, $p<.05$. For the ADHD group a negative correlation was found between rTPJ activation and omissions, $r(44)=-.32$, $p<.05$, and between SMA activation and CV, $r(44)=-.41$, $p<.01$. For P3 sources, the TD group showed statistical trends for negative correlations between activation in both ACC and SMA and SSRT, $r(49)=-.31$ and -.28 respectively, $p<.05$. For the ADHD group a negative correlation was found between SMA activation and SSRT, $r(44)=-.37$, $p<.05$. No significant correlations were found between source activations and ADHD symptoms.

Failed Inhibition. For N2 sources, only the ADHD group showed a relation between rIFG activation and SSRT, $r(44)=-.33$, $p<.05$. No significant correlations were found between source activations and ADHD symptoms.

Table II. GLM MANOVAs of mean ERP amplitudes for the TD and ADHD groups for SI and FI

		TD		ADHD		Location (L)		Condition (C)		Group (G)		C x L		C x G		C x L x G	
		SI	FI	SI	FI	*F*	η_p^2	*F*	η_p^2	*F*	η_p^2	*F*	η_p^2	*F*	η_p^2	*F*	η_p^2
N1	Fz	-4.1(3.3)	-2.8(3.3)	-4.1(3.4)	-3.7(3.8)	52.61***	.53	3.56	.04	1.09	0.1	2.08	.04	0.03	.00	4.34*	.09
	Cz	-3.0(4.1)	-2.6(3.6)	-3.9(3.5)	-2.6(3.6)												
	Pz	0.0(4.3)	0.1(3.6)	-1.1(4.2)	-0.5(3.8)												
P2	Fz	1.6(4.8)	2.2(6.3)	3.1(5.2)	3.2(5.4)	0.93	.02	0.26	.00	0.68	.01	6.90**	.13	0.38	.00	2.25	.05
	Cz	2.5(5.4)	2.0(5.7)	2.8(5.6)	3.3(5.5)												
	Pz	2.9(5.7)	1.5(5.3)	2.7(5.9)	2.2(5.8)												
N2	LF	-1.3(6.0)	-2.4(6.6)	2.3(5.4)	1.1(6.3)	6.92***	.18	20.35***	.18	10.95**	.10	2.51	.08	0.01	0.00	0.63	.02
	LP	-1.4(6.1)	-3.8(5.7)	1.7(5.3)	-0.1(4.9)												
	RF	-1.5(6.6)	-2.8(6.9)	1.7(6.1)	0.2(6.9)												
	RP	-3.2(7.3)	-5.3(6.9)	0.9(6.0)	-1.1(5.7)												
P3	Fz	6.2(10.1)	3.9(10.7)	4.2(6.9)	4.6(7.6)	38.98***	.45	10.45**	.10	1.49	.02	2.08	.04	6.90*	.07	2.92	.06
	Cz	11.0(9.0)	7.9(8.9)	7.1(7.6)	7.0(9.1)												
	Pz	14.7(8.6)	12.2(7.6)	11.4(9.0)	10.2(9.6)												

Note. Data presented are mean(SD) in μV; df(1,95) for Group, Condition and CxG, df(2,94) for Location, CxL, and CxLxG except for N2 df(3,93). ERP = event-related potential; TD = typically developing; SI = successful inhibition; FI = failed inhibition; LF = left frontal; LP = left parietal; RF = right frontal; RP = right parietal.

*p<.05, **p<.01, ***p<.001

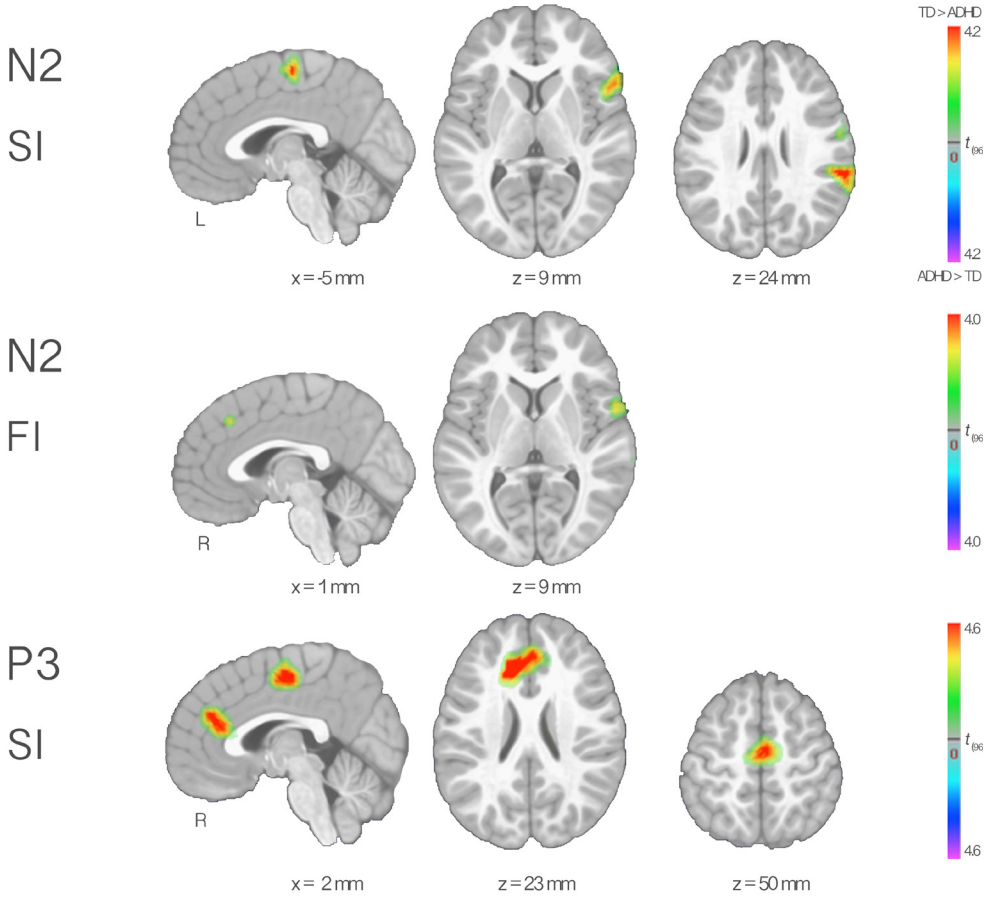

Figure 2. Significant differences between ADHD and TD in LAURA source estimations over the analysis windows of N2 during SI and FI, and P3 during SI, shown on a paediatric MNI template brain.

Note. Illustrated coordinates were converted from MNI to Talairach space. Colour indicates the t-values. Lower bound Bonferroni-corrected significance is $p<.0004$. For viewing purposes, images were interpolated with the 4NN method. TD = typically developing; SI = successful inhibition; FI = failed inhibition; MNI = Montreal Neurological Institute; 4NN = 4-nearest-neighbor.

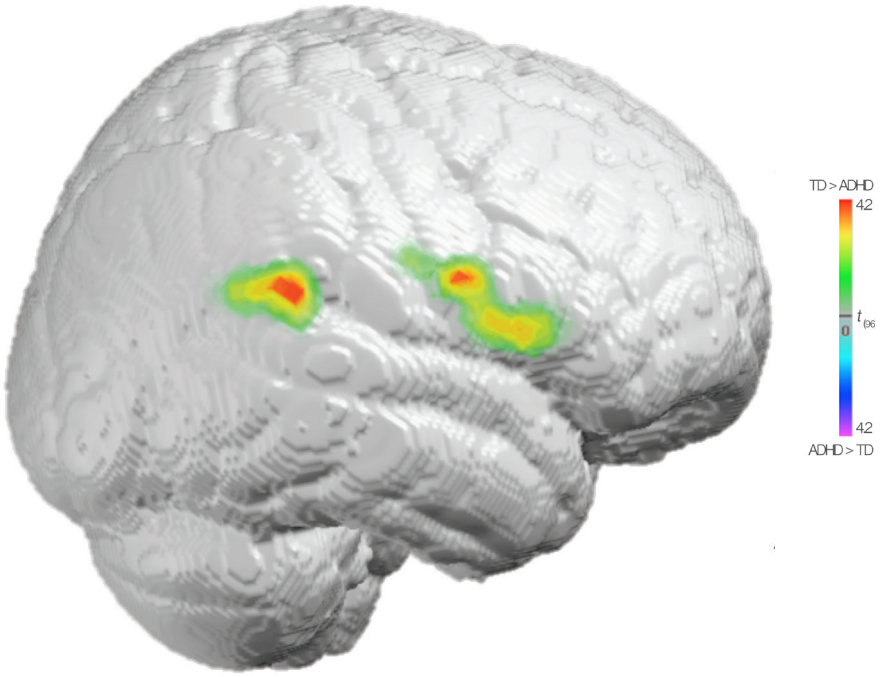

Figure 3. Lateral view of a three-dimensional rendering of the paediatric MNI template brain with significant differences between ADHD and TD in LAURA source estimations over the N2 analysis window during SI. *Note.* Colour indicates the t-values. Lower bound Bonferroni-corrected significance is $p<.0004$. For viewing purposes, images were interpolated with the 4NN method. TD = typically developing; SI = successful inhibition; MNI = Montreal Neurological Institute; 4NN = 4-nearest-neighbor.

DISCUSSION

The present study aimed to critically appraise processes involved in response inhibition as assessed with the SST in children with ADHD compared to typically developing children. Overall, earlier processing steps as reflected in N1 and P2 did not differentiate between ADHD and TD, except for a success-related N1 modulation that was only apparent in the ADHD group; however, later N2 and P3 components were reduced in amplitude in ADHD, as hypothesized. Differentiating components were localized in both typical inhibition and ventral attention (N2), and monitoring networks (P3). Surprisingly, while groups differed on MRT, CV and number of omissions, SSRTs were equal among groups (250ms).

Performance data indicated difficulties with processing speed and/or attention (increased MRT, more omission errors and increased CV), which are characteristic for ADHD (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006). Although many behavioural studies found evidence for slower SSRTs (Alderson et al., 2007), several ERP studies also failed to find this difference (Johnstone et al., 2007; Liotti et al., 2005; Pliszka, Liotti, & Woldorff, 2000b). This could be due to intrinsic characteristics of ERP tasks, such as a large number of trials administered, differences in inter-trial-intervals during the task or test environment.

In contrast to previous findings, no marked deficiencies in early processing were identified in children with ADHD, although a success-related N1 modulation was only apparent in the ADHD group with increased N1 for SI at the vertex compared to FI. Possibly, children with ADHD partly compensate for inhibitory or attentional difficulties by increasing sensory processing of the stop stimulus to enable successful stopping. Several factors could explain the inconsistent findings of the few studies that have looked into early components in the SST. Three of the available four studies used an auditory stop-signal (Dimoska et al., 2003; Johnstone et al., 2007; Senderecka et al., 2012). Possibly, abnormal sensory registration in ADHD is modality-specific, at least for the N1 and P2 components. Another explanation is the lack of correction for overlap between go and stop ERPs in two studies (Johnstone et al., 2007; Senderecka et al., 2012), or residual overlap despite weighted stop-delay sub-ranges, which is a method to control but not correct differential overlap (Dimoska et al., 2003; Shen et al., 2011).

In line with previous studies, N2 amplitudes were reduced in ADHD (Albrecht, Banaschewski, Brandeis, Heinrich, & Rothenberger, 2005; Dimoska et al., 2003; Johnstone et al., 2007; Liotti et al., 2007, 2010; Pliszka et al., 2007). Group differences in individual distributed source imaging estimations revealed decreased activation in the rIFG (BA 44) for both SI and FI, and specifically for SI, reduced activation in the rTPJ and SMA in the ADHD group.

Reduced activations in the rIFG and SMA have been identified in numerous SST imaging studies in children with ADHD (Hart et al., 2013; McCarthy, Skokauskas, & Frodl, 2014). Aron et al. (2007) proposed that the rIFG implements inhibition via the subthalamic nucleus (STN), which activates the globus pallidus, resulting in thalamo-motorcortical inhibition. However, the rIFG has also been associated with a right-lateralized ventral attention network together with the rTPJ, which is important for responding to behaviourally relevant stimuli and maintaining attentive control (Corbetta, Patel, & Shulman, 2008; Hampshire et al., 2010; Singh-Curry & Husain, 2009). A tentative conclusion would be that the findings of reduced activation in both rIFG and rTPJ in the ADHD group, and the lack of SSRT differences, support the second interpretation, that the ventral attention network is disrupted. However, the relation between activation in rTPJ and rIFG and performance measures may point to a dissociation between attention and inhibition, as within the ADHD group, the rTPJ was related to omissions on go trials, and for both groups rIFG was related to SSRT.

The role of the (pre-)SMA in inhibition is still debated. There is evidence for connections between the pre-SMA, rIFG and STN, in which the pre-SMA could implement neural inhibition directly or have a conflict monitoring function (Aron et al., 2007). The former option is supported by transcranial magnetic stimulation (TMS) studies experimentally disrupting pre-SMA functioning during a SST resulting in slower SSRTs (Chen, Muggleton, Tzeng, Hung, & Juan, 2009; Obeso, Robles, Marrón, & Redolar-Ripoll, 2013). Sharp et al. (2010) even suggest a unique role of the pre-SMA in inhibition. Others argue that the pre-SMA is implicated in the complexity of condition-action associations or switching between tasks (Nachev, Kennard, & Husain, 2008) The subsequent P3 results were in accordance with other studies, showing success-related enhancement during SI and reduced amplitudes during SI in children with ADHD (Johnstone et al., 2007; Liotti et al., 2007, 2010; Pliszka et al., 2007). Furthermore, P3 differences between groups were localized in medial frontal brain areas, ACC and SMA, which play important roles in cognitive control. A recent overarching theory of the ACC proposes that this structure allocates control based on an evaluation of the expected value of control (EVC) (Shenhav, Botvinick, & Cohen, 2013). The EVC can be seen as a cognitive control signal based on diverse sources of information, such as expected pay-off of not implementing control and costs in terms of effort to implement control.

Some limitations to this study should be noted. First, source imaging is an estimation of brain activity instead of a measurement like fMRI, with less spatial resolution, and should therefore be interpreted with more caution. Second, distributed source imaging can produce

spurious activations, or 'ghost' sources (Fuchs, Wagner, Kohler, & Wischmann, 1999). However, both problems were reduced in the current study by calculating individual source estimations, which make it unlikely that spurious activations will be consistently observed across individuals, and stringent statistical group comparisons give more confidence than source localization of grand averages. At last, although we found a significant interaction between group and condition for the P3 amplitude measures, further post-hoc tests revealed a statistical trend for a difference (p=.055) between groups on successful inhibition trials. The P3 amplitudes showed considerable variation within groups, which may explain we only found a trend.

In conclusion, although we found no evidence for deficient early processing, children with ADHD may partly compensate for inhibitory or attentional difficulties by intensifying sensory processing to enable successful stopping. There were marked differences in subsequent N2 and P3 processing stages, which were localized in a right lateralized network encompassing rTPJ and rIFG, and medial frontal areas, including ACC and SMA, respectively. These areas strikingly coincide with fMRI evidence of the SST in ADHD (Hart et al., 2013; McCarthy et al., 2014). We speculate that disruptions in the ventral attention network during N2 at least contribute to poor performance of children with ADHD on the SST. These disruptions seem to be followed by deficient monitoring of the success of inhibition as reflected by P3. However, the functional specificity of these networks remains to be better established.

REFERENCES

Albrecht, B., Banaschewski, T., Brandeis, D., Heinrich, H., & Rothenberger, A. (2005). Response inhibition deficits in externalizing child psychiatric disorders: an ERP-study with the Stop-task. *Behavioral and Brain Functions, 1*, 22. doi:10.1186/1744-9081-1-22

Alderson, R., Rapport, M., & Kofler, M. (2007). Attention-deficit/hyperactivity disorder and behavioral inhibition: a meta-analytic review of the stop-signal paradigm. J*ournal of Abnormal Child Psychology, 35*(5), 745–758. doi:10.1007/s10802-007-9131-6

Aron, A., Behrens, T., Smith, S., Frank, M., & Poldrack, R. (2007). Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. *The Journal of Neuroscience, 27*(14), 3743–3752. doi:10.1523/JNEUROSCI.0519-07.2007

Barkley, R. A. (1997). Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychological Bulletin*, 121(1), 65–94.

Bekker, E. M., Kenemans, J. L., Hoeksma, M. R., Talsma, D., & Verbaten, M. N. (2005). The pure electrophysiology of stopping. *International Journal of Psychophysiology, 55*(2), 191–8. doi:10.1016/j.ijpsycho.2004.07.005

Bokura, H., Yamaguchi, S., & Kobayashi, S. (2001). Electrophysiological correlates for response inhibition in a Go/NoGo task. *Clinical Neurophysiology, 112*(12), 2224–32.

Castellanos, F. X., Sonuga-Barke, E. J. S., Milham, M. P., & Tannock, R. (2006). Characterizing cognition in ADHD: beyond executive dysfunction. *Trends in Cognitive Sciences, 10*(3), 117–23. doi:10.1016/j.tics.2006.01.011

Chen, C.-Y., Muggleton, N. G., Tzeng, O. J. L., Hung, D. L., & Juan, C.-H. (2009). Control of prepotent responses by the superior medial frontal cortex. *NeuroImage, 44*(2), 537–45. doi:10.1016/j.neuroimage.2008.09.005

Corbetta, M., Patel, G., & Shulman, G. L. (2008). The reorienting system of the human brain: from environment to theory of mind. *Neuron, 58*(3), 306–24. doi:10.1016/j.neuron.2008.04.017

Corp IBM. (2011). IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.

Crottaz-Herbette, S., & Menon, V. (2006). Where and when the anterior cingulate cortex modulates attentional response: combined fMRI and ERP evidence. J*ournal of Cognitive Neuroscience, 18*(5), 766–80. doi:10.1162/jocn.2006.18.5.766

Dennis, M., Francis, D. J., Cirino, P. T., Schachar, R., Barnes, M. a, & Fletcher, J. M. (2009). Why IQ is not a covariate in cognitive studies of neurodevelopmental disorders. *Journal of the International Neuropsychological Society, 15*(3), 331–343. doi:10.1017/S1355617709090481

Dimoska, A., Johnstone, S., Barry, R., & Clarke, A. R. (2003). Inhibitory motor control in children with attention-deficit/hyperactivity disorder: event-related potentials in the stop-signal paradigm. *Biological Psychiatry, 54*(12), 1345–54. doi:S0006322303007030

Enriquez-Geppert, S., Konrad, C., Pantev, C., & Huster, R. J. (2010). Conflict and inhibition differentially affect the N200/P300 complex in a combined go/nogo and stop-signal task. *NeuroImage, 51*(2), 877–87. doi:10.1016/j.neuroimage.2010.02.043

Fonov, V., Evans, A. C., Botteron, K., Almli, C. R., McKinstry, R. C., & Collins, D. L. (2011). Unbiased average age-appropriate atlases for pediatric studies. *NeuroImage, 54*(1), 313–27. doi:10.1016/j.neuroimage.2010.07.033

Fonov, V., Evans, A. C., McKinstry, R. C., Almli, C. R., & Collins, D. (2009). Unbiased nonlinear average age-appropriate brain templates from birth to adulthood. *NeuroImage, 47*, S102. doi:10.1016/S1053-8119(09)70884-5

Frazier, T. W., Demaree, H. a, & Youngstrom, E. a. (2004). Meta-analysis of intellectual and neuropsychological test performance in attention-deficit/hyperactivity disorder. *Neuropsychology, 18*(3), 543–555. doi:10.1037/0894-4105.18.3.543

Fuchs, M., Wagner, M., Kohler, T., & Wischmann, H. (1999). Linear and Nonlinear Current Density Reconstructions. *Journal of Clinical Neurophysiology, 16*(3), 267–295.

Grave de Peralta Menendez, R., Gonzalez Andino, S., Lantz, G., Michel, C. M., & Landis, T. (2001). Noninvasive localization of electromagnetic epileptic activity. I. Method descriptions and simulations. *Brain Topography, 14*(2), 131–7.

Grave de Peralta Menendez, R., Murray, M. M., Michel, C. M., Martuzzi, R., & Gonzalez Andino, S. L. (2004). Electrical neuroimaging based on biophysical constraints. *NeuroImage, 21*(2), 527–39. doi:10.1016/j.neuroimage.2003.09.051

Hampshire, A., Chamberlain, S. R., Monti, M. M., Duncan, J., & Owen, A. M. (2010). The role of the right inferior frontal gyrus: inhibition and attentional control. *NeuroImage, 50*(3), 1313–1319. doi:10.1016/j.neuroimage.2009.12.109

Hart, H., Radua, J., Nakao, T., Mataix-Cols, D., & Rubia, K. (2013). Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. *JAMA Psychiatry, 70*(2), 185–198. doi:10.1001/jamapsychiatry.2013.277

Johnstone, S., Barry, R., & Clarke, A. R. (2007). Behavioural and ERP indices of response inhibition during a Stop-signal task in children with two subtypes of Attention-Deficit Hyperactivity Disorder. International *Journal of Psychophysiology, 66*(1), 37–47. doi:10.1016/j.ijpsycho.2007.05.011

Jung, T. P., Makeig, S., Humphries, C., Lee, T. W., McKeown, M. J., Iragui, V., & Sejnowski, T. J. (2000). Removing electroencephalographic artifacts by blind source separation. *Psychophysiology, 37*(2), 163–178.

Laird, A. R., Fox, P. M., Price, C. J., Glahn, D. C., Uecker, A. M., Lancaster, J. L., … Fox, P. T. (2005). ALE meta-analysis: controlling the false discovery rate and performing statistical contrasts. *Human Brain Mapping, 25*(1), 155–64. doi:10.1002/hbm.20136

Lancaster, J. L., Tordesillas-Gutiérrez, D., Martinez, M., Salinas, F., Evans, A., Zilles, K., … Fox, P. T. (2007). Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. *Human Brain Mapping, 28*(11), 1194–205. doi:10.1002/hbm.20345

Lavric, A., Pizzagalli, D. a, & Forstmeier, S. (2004). When “go” and “nogo” are equally frequent: ERP components and cortical tomography. *The European Journal of Neuroscience, 20*(9), 2483–8. doi:10.1111/j.1460-9568.2004.03683.x

Lijffijt, M., Kenemans, J. L., Verbaten, M. N., & van Engeland, H. (2005). A meta-analytic review of stopping performance in attention-deficit/hyperactivity disorder: deficient inhibitory motor control? Journal of Abnormal Psychology, 114(2), 216–222. doi:10.1037/0021-843X.114.2.216

Liotti, M., Pliszka, S. R., Higgins, K., Perez, R., & Semrud-Clikeman, M. (2010). Evidence for specificity of ERP abnormalities during response inhibition in ADHD children: a comparison with reading disorder children without ADHD. Brain and Cognition, 72(2), 228–37. doi:10.1016/j.bandc.2009.09.007

Liotti, M., Pliszka, S. R., Perez, R., Kothmann, D., & Woldorff, M. G. (2005). Abnormal brain activity related to performance monitoring and error detection in children with ADHD. Cortex, 41(3), 377–88.

Liotti, M., Pliszka, S. R., Perez, R., Luus, B., Glahn, D., & Semrud-Clikeman, M. (2007). Electrophysiological correlates of response inhibition in children and adolescents with ADHD: influence of gender, age, and previous treatment history. Psychophysiology, 44(6), 936–48. doi:10.1111/j.1469-8986.2007.00568.x

Logan, G. (1994). On the ability to inhibit thought and action: A users' guide to the stop signal paradigm. (T. H. Carr & D. Dagenbach, Eds.). San Diego: Academic Press.

Logan, G., & Cowan, W. (1984). On the ability to inhibit simple and choice reaction time responses: a theory of an act of control. Psychological Review, 91(3), 295–327.

Logan, G., Cowan, W., & Davis, K. (1984). On the ability to inhibit simple and choice reaction time responses: a model and a method. Journal of Experimental Psychology. Human Perception and Performance, 10(2), 276–291.

McCarthy, H., Skokauskas, N., & Frodl, T. (2014). Identifying a consistent pattern of neural function in attention deficit hyperactivity disorder: a meta-analysis. Psychological Medicine, 44(4), 869–880. doi:10.1017/S0033291713001037

Michel, C. M., Murray, M. M., Lantz, G., Gonzalez, S., Spinelli, L., & Grave de Peralta Menendez, R. (2004). EEG source imaging. Clinical Neurophysiology, 115(10), 2195–222. doi:10.1016/j.clinph.2004.06.001

Nachev, P., Kennard, C., & Husain, M. (2008). Functional role of the supplementary and pre-supplementary motor areas. Nature Reviews, 9(11), 856–69. doi:10.1038/nrn2478

Nieuwenhuis, S., Yeung, N., van den Wildenberg, W., & Ridderinkhof, K. R. (2003). Electrophysiological correlates of anterior cingulate function in a go/no-go task: effects of response conflict and trial type frequency. Cognitive, Affective & Behavioral Neuroscience, 3(1), 17–26. doi:10.3758/CABN.3.1.17

Obeso, I., Robles, N., Marrón, E. M., & Redolar-Ripoll, D. (2013). Dissociating the Role of the pre-SMA in Response Inhibition and Switching: A Combined Online and Offline TMS Approach. Frontiers in Human Neuroscience, 7(April), 150. doi:10.3389/fnhum.2013.00150

Oosterlaan, J., Logan, G. D., & Sergeant, J. A. (1998). Response inhibition in AD/HD, CD, comorbid AD/HD + CD, anxious, and control children: a meta-analysis of studies with the stop task. Journal of Child Psychology and Psychiatry, 39(3), 411–425.

Pauls, A., O'Daly, O., Rubia, K., Riedel, W., Williams, S., & Mehta, M. (2012). Methylphenidate effects on prefrontal functioning during attentional-capture and response inhibition. Biological Psychiatry, 72(2), 142–149. doi:10.1016/j.biopsych.2012.03.028

Pelham, W. E., Gnagy, E. M., Greenslade, K., & Milich, R. (1992). Teacher ratings of DSM-III-R symptoms for

the disruptive behaviour disorder. *Journal of the American Academy of Child & Adolescent Psychiatry, 31*(2), 210–218.

Perrin, F., Pernier, J., Bertrand, O., & Echallier, J. F. (1989). Spherical splines for scalp potential and current density mapping. *Electroencephalography and Clinical Neurophysiology, 72*(2), 184–7.

Pizagalli, D. A. (2007). Electroencaphalography and high-density electrophysiological source localization. In J. T. Cacioppo, L. G. Tassinary, & G. Berntson (Eds.), *Handbook of Psychophysiology* (3rd ed., pp. 56–84). Cambridge University Press.

Pliszka, S. R., Liotti, M., Bailey, B. Y., Perez, R., Glahn, D., & Semrud-Clikeman, M. (2007). Electrophysiological effects of stimulant treatment on inhibitory control in children with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology*, 17(3), 356–66. doi:10.1089/cap.2006.0081

Pliszka, S. R., Liotti, M., & Woldorff, M. G. (2000a). Inhibitory control in children with attention-deficit/hyperactivity disorder: event-related potentials identify the processing component and timing of an impaired right-frontal response-inhibition mechanism. *Biological Psychiatry, 48*(3), 238–46. doi:S0006-3223(00)00890-8 [pii]

Ramautar, J. R., Kok, A., & Ridderinkhof, K. R. (2004). Effects of stop-signal probability in the stop-signal paradigm: the N2/P3 complex further validated. *Brain Cogn, 56*(2), 234–252. doi:10.1016/j.bandc.2004.07.002

Senderecka, M., Grabowska, A., Szewczyk, J., Gerc, K., & Chmylak, R. (2012). Response inhibition of children with ADHD in the stop-signal task: an event-related potential study. *International Journal of Psychophysiology, 85*(1), 93–105. doi:10.1016/j.ijpsycho.2011.05.007

Shaffer, D., Fisher, P., Lucas, C. P., Dulcan, M. K., & Schwab-Stone, M. E. (2000). NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. *Journal of the American Academy of Child and Adolescent Psychiatry, 39*(1), 28–38. doi:10.1097/00004583-200001000-00014

Sharp, D., Bonnelle, V., De Boissezon, X., Beckmann, C., James, S., Patel, M., & Mehta, M. (2010). Distinct frontal systems for response inhibition, attentional capture, and error processing. *Proceedings of the National Academy of Sciences of the United States of America, 107*(13), 6106–6111. doi:10.1073/pnas.1000175107

Shen, I.-H., Tsai, S.-Y., & Duann, J.-R. (2011). Inhibition control and error processing in children with attention deficit/hyperactivity disorder: an event-related potentials study. *International Journal of Psychophysiology, 81*(1), 1–11. doi:10.1016/j.ijpsycho.2011.03.015

Shenhav, A., Botvinick, M. M., & Cohen, J. D. (2013). The expected value of control: an integrative theory of anterior cingulate cortex function. *Neuron, 79*(2), 217–240. doi:10.1016/j.neuron.2013.07.007

Singh-Curry, V., & Husain, M. (2009). The functional role of the inferior parietal lobe in the dorsal and ventral stream dichotomy. *Neuropsychologia, 47*(6), 1434–48. doi:10.1016/j.neuropsychologia.2008.11.033

Sonuga-Barke, E. J. S., 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. *Journal of the American Academy of Child & Adolescent Psychiatry, 49*(4), 345–355.

doi:10.1016/j.jaac.2009.12.018

Swanson, J., Schuck, S., Mann, M., & Carlson, C. (2006). Categorical and dimensional definitions and evaluations of symptoms of ADHD: The SNAP and SWAN Rating Scales. University of California, Irvine.

Van Boxtel, G. J., van der Molen, M. W., Jennings, J. R., & Brunia, C. H. (2001). A psychophysiological analysis of inhibitory motor control in the stop-signal paradigm. *Biological Psychology, 58*(3), 229–62.

Verbruggen, F., Chambers, C. D., & Logan, G. D. (2013). Fictitious inhibitory differences: how skewness and slowing distort the estimation of stopping latencies. *Psychological Science, 24*(3), 352–362. doi:10.1177/0956797612457390

Wechsler, D. (1991). Weschler intelligence scale for children - third edition. Psychological Corporation, San Antonio, TXC.

Woldorff, M. G. (1993). Distortion of ERP averages due to overlap from temporally adjacent ERPs: analysis and correction. *Psychophysiology, 30*(1), 98–119.