SPECIAL ISSUE

ABNORMAL BRAIN ACTIVITY RELATED TO PERFORMANCE MONITORING AND ERROR DETECTION IN CHILDREN WITH ADHD

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ABSTRACT

Brain electrical activity associated with inhibitory control was recorded in ten ADHD and ten healthy children using high density event related potentials (ERPs) during the Stop Signal Task (SST). SST is a two-choice reaction time (RT) paradigm, in which subjects are required, on 25% of the trials, to withdraw their response upon presentation of a "Stop Signal". In the healthy children, the ERP evoked by the Stop Signal differed for successful inhibitions (SI) compared to failed inhibitions (FI), with greater amplitude of a positive wave peaking around 320 msec over anterior medial frontal scalp (P3a). Such success-related P3a activity was significantly reduced in amplitude in the ADHD group. In addition, the error related negativity (ERN), a sharp negative wave that is present selectively on error trials in choice RT experiments, peaking 100 ms after motor onset, and distributed over anterior medial frontal scalp, was also markedly reduced in the ADHD group. The scalp distribution of the group differences in P3a and the ERN is consistent with a reduction of activity of sources in dorsal anterior cingulate cortex (dACC), suggesting a global deficit in cognitive control operations subserved by dACC in ADHD.

Key words: ERPs, ADHD, response inhibition, anterior cingulate, error detection, N200, P3a, ERN, stop signal task

INTRODUCTION

Children with Attention Deficit-Hyperactivity Disorder (ADHD) perform more poorly than controls and children with other psychiatric disorders on tasks that measure inhibitory control, such as the Continuous Performance Task (CPT) and the Stop Signal Task (Logan et al., 1984; Schachar et al., 1990; van der Meere et al., 1992; Pliszka et al., 1997). A fundamental deficit in inhibitory control mechanisms has therefore been hypothesized to be at the core of the syndrome (Barkley, 1997). Based on *in vivo* morphometric evidence of MRI abnormalities in right frontal cortex and caudate nuclei (Castellanos et al., 1996; Filipek et al., 1997), it has been proposed that abnormalities in a right-sided striato-frontal network may be responsible for the deficits in inhibitory control in ADHD (Castellanos, 1997; Casey et al., 1997a).

Recent functional MRI (fMRI) studies in healthy adults and children have confirmed that the right middle and right inferior frontal gyri are implicated during tasks involving response inhibition (Go/NoGo, WCST, etc: Garavan et al., 1999; Casey et al., 1997b; Rubia et al., 1999). A recent lesion-correlation study has shown that patients with lesions of the pars triangularis of the right inferior frontal gyrus (Brodmann area 45) have a selective deficit in response inhibition in the Stop Signal Task (Aron et al., 2003).

Consistent with the proposed model (Castellanos, 1997), an fMRI study using the Stop Signal Task in a block design found that ADHD adolescents did not show the activation of right middle and inferior frontal gyrus observed in healthy adolescents (Rubia et al., 1999). Note however that a fMRI study employing a Go/NoGo task found more activation in lateral prefrontal cortex in ADHD children off stimulant medication relative to healthy control children (Vaidya et al.,1998).

Using high-density event-related potentials (ERPs), we previously (Pliszka et al., 2000) reported applying the Stop Signal Task in ADHD and healthy children and finding that a right inferior frontal N200 in response to the Stop Signal was strikingly reduced in the ADHD children, suggesting that a right prefrontal mechanism may operate very early (200 msec) to trigger inhibitory control (see Figure 1). This combined evidence points to a crucial role of the right lateral prefrontal cortex in response inhibition during tasks of cognitive control.

Other evidence in the literature points to an additional involvement of *midline* prefrontal cortex, in particular the right dorsal anterior cingulate cortex (dACC), in components of executive function and inhibitory control. The crucial role of right dACC in tasks of response selection and conflict monitoring (such as the Stroop task), has been firmly established by PET, fMRI, ERP and lesion correlation studies (Pardo et al., 1990; Carter et al., 1995; Liotti et al., 2000; Swick and Jonanovic, 2002). Of importance here, dACC activations have recently been reported in healthy adults and adolescents during Go/NoGo tasks by event-related techniques, both with ERPs and fMRI (Liddle et al., 2001; Garavan et al., 2002).

A partial report of this study was presented at the Cognitive Neuroscience Society annual meeting, New York, March 30th-April 1st 2003.

Casey et al (1997a) found a significant correlation between children's performance in a difficult visual search task and the volume of the right dACC (Casey et al., 1997c).

Another rich body of evidence associates medial prefrontal cortex, particularly dACC, with error processing (error detection and correction) during action monitoring in Go/NoGo tasks and other effortful attention tasks (Stroop task, Eriksen flanker task) using ERPs (Gehring et al., 2001; Liotti et al., 2001; Luu et al., 2003; Bush et al., 2000). The Error-related negativity (ERN) is a sharp transient ERP difference wave observed when the ERP to correct responses (Hits) is subtracted from the ERP to incorrect responses (i.e., errors). The ERN is time-locked to the onset of the motor response, peaking at around 60-80 msec after the onset of a button press, and has a scalp topography over midline anterior frontal scalp. Source dipole modeling and recent event-related fMRI studies have confirmed that the main source of error-related activity is in dorsal ACC (Kiehl et al., 2000; Garavan et al., 2002). It has been hypothesized that the ERN reflects a mechanism that monitors and checks a representation of the intended response to a representation of the actual response (Bernstein et al., 1995). It has also been argued that the ERN reflects a more general error detection mechanism rather than a mechanism involved in error correction (Coles et al., 1998). More recently, it has been proposed that the ERN may be related to motivation and/or the affective processing involved in error detection and correction. The ERN amplitude is increased when task instructions emphasize accuracy over speed (Gehring and Fencsik, 1999). Importantly, ERP studies of error processing through the ERN paradigm have provided some of the best evidence for the role of dACC in cognitive function, recently prompting a lively debate about the functional role of this structure in general conflict monitoring in cognitive control versus error detection (Botvinick et al., 1999, 2001; Van Veen and Carter, 2002b).

In regard to the relevance of dACC function in ADHD, an fMRI study found that adults with ADHD performing the Counting Stroop Task failed to show the activation of dACC that is observed in adult healthy comparisons (Bush et al., 1999). Furthermore, an fMRI study using a block design in ADHD adolescents showed no activation in right dACC during response inhibition in the Stop Signal Task, while such activity was present in healthy adolescents (Rubia et al., 1999). These studies suggest that dACC is involved *both* in conflict monitoring in the Stroop Task, and in components of inhibitory control in Go/NoGo tasks. However, to date no studies have explored error processing with the ERN paradigm in ADHD children.

Although available research suggests a role of midline frontal structures in inhibitory control and error processing in healthy subjects and abnormal activation of such structures in inhibitory control tasks in ADHD children, the specific processing component affected and the time course of its activation are unknown.

The present study aimed at clarifying aspects of normal and abnormal functional organization of inhibitory control and error processing in children with ADHD and healthy children. A specific prediction was that the Error-Related Negativity (ERN) would be abnormally reduced in ADHD children relative to controls, reflecting a global deficit in cognitive control functions supported by the midline frontal structures.

Previous fMRI studies in ADHD adolescents and adults had used *blocked* fMRI designs (Bush et al., 1999; Rubia et al., 1999), and were therefore unable to separate activity related to Successful and Failed inhibitory control, nor to separate activity related to correct responses and Errors to Go trials (ERN activity). In the present study, high-density ERPs were employed in ADHD and healthy children during performance of the Stop Signal Task.

Event Related Potentials are msec by msec reflections of sensory, motor, and cognitive processing during the unfolding of cognitive tasks. They are extracted from the background electroencephalogram (EEG) through a process of time-locked averaging of many trials of the same type to the onset of a sensory stimulus or a motor response. ERPs consist of an ordered sequence of waveforms identified as P100, N100, P200, N200, P300, depending on their latency and their polarity. Early components (P100 and N100) are called exogenous, because they require a stimulus, and reflect activity in primary or secondary sensory areas. However, such early ERP waves can be modulated by sustained attention and top-down cognitive control processes (Hillyard and Kutas, 1983; Woldorff et al., 2002). A longer latency component, the high amplitude P3 or P300, is called endogenous, because it can be present even in response to an expected missing stimulus. P300 is elicited in visual or auditory oddball tasks in response to task-relevant, salient infrequent targets, with greater amplitude over posterior (parietal) scalp (see Hillyard and Kutas, 1983, for a review). Another waveform of interest is the N200. A prominent N200 with a frontal distribution is observed in response to NoGo stimuli in Go/NoGo tasks, and it is thought to reflect response inhibition processes. In contrast, Go stimuli elicit the parietally distributed P300 (Falkenstein et al., 1999).

Event related potentials (ERPs) possess extremely high temporal resolution (milliseconds), and have the potential to identify the timing, order of activation, and dynamic orchestration of brain regions during the unfolding of cognitive tasks, including the Stop Signal task. Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI), in contrast, allow for precise localization of functional activations during cognitive tasks, but their temporal resolution is

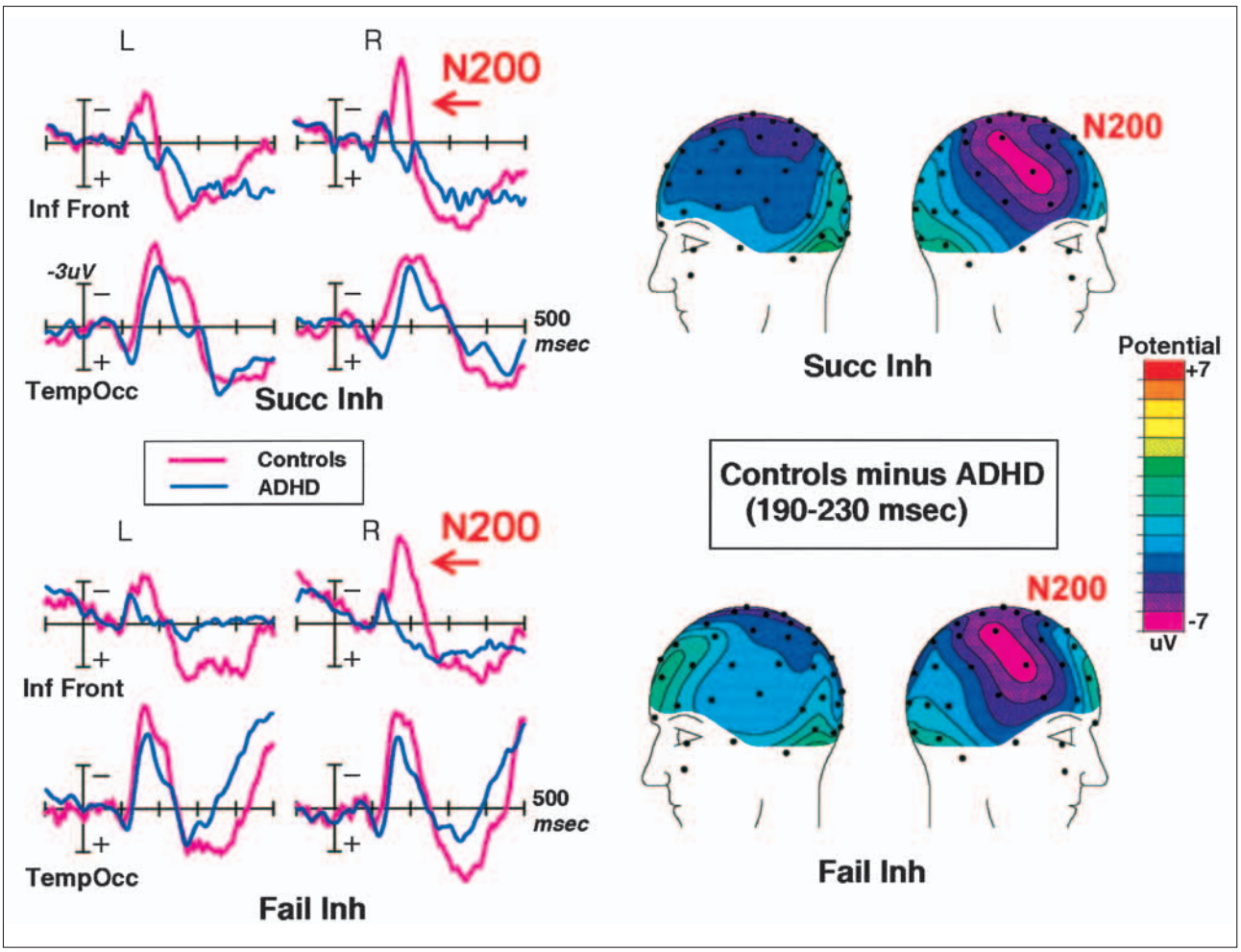

Fig. 1 – *N200 to the Stop Signal (190-220 msec). Left: Grand average ERPs for Control (purple) and ADHD (blue) for Successful Inhibition (Succ Inh, top) and Failed Inhibition trials (Fail Inh, bottom), for inferior frontal (anterior) and parieto-occipital (posterior) scalp regions. L = left; R = right. Zero point is the Stop signal onset. Right: Topographic maps of the ERP difference wave for Controls minus ADHD for Successful Inhibition trials (Succ Inh, top) and Failed Inhibition trials (Fail Inh, bottom). Note the focal distribution of this difference wave over right inferior frontal scalp for both Successful Inhibitions and Failed Inhibition trials (Reproduced with permission of the Society for Biological Psychiatry).*

limited by the slow time course of the hemodynamic response.

However, spatial resolution of the ERP method is only coarse – albeit somewhat improved by the use of high-density sensor arrays. Given certain scalp distributions of ERP effects, one cannot assume that ERP scalp topography equates to localization of underlying electrical generators. Identification of the cortical generators of the scalp recorded ERP components relies on dipole source modeling, a complex task in the presence of multiple dipoles, since in that case there are no unique solutions. The most successful attempts at EEG dipole source analysis employ realistic head models (e.g., brain MRI data from the same subject/s), or the within-subject, combined use of ERPs and fMRI or PET during the same cognitive tasks, with PET or fMRI regional activations used as seeds to constrain ERP dipole modeling (e.g., Woldorff et al., 2002).

Another advantage of ERPs is that, along with the recently developed Event-Related fMRI, they allow selective averaging of different stimulus types within the same experimental block, allowing *mixed*-trial analysis (such as Successful and Failed inhibitions in the Stop Signal Task). In contrast, PET and conventional fMRI only allow *block* paradigm design, and have no temporal resolution. Because of the slowness of the hemodynamic response (peaking 5 sec after an event and subsiding after 12-15 sec, and affecting both blocked and event-related fMRI designs), ERPs and the magnetic equivalent ERFs (event related fields) can provide unique temporal information concerning the timing and order of activations of normal and abnormal neural activity during the unfolding of cognitive tasks.

In summary, the present study aimed at clarifying spatio-temporal aspects of normal and abnormal functional organization of inhibitory control and error processing in ADHD and healthy children using high density ERPs during the performance of the Stop Signal Task. The emphasis is on ERP findings possibly associated to midline frontal function. A partial report of this investigation in the same cohorts of subjects, focusing on a right inferior frontal N200 abnormality in ADHD, has been published elsewhere (Pliszka et al., 2000) (see Figure 1).

Methods

Subjects

Ten boys with ADHD, Combined Type, and ten age-matched control boys served as subjects in the ERP study (9-11 yrs old). All subjects were right handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). Diagnosis of ADHD was established by the Diagnostic Interview Schedule for Children-Parent Version (DISC) (Shaffer et al., 1996). ADHD, Combined Type, is defined as having at least six of nine symptoms of inattention/distractibility and at least six of nine symptoms of hyperactivity/impulsivity as defined by the fourth edition of the Diagnostic and Statistical Manual of American Psychiatric Association (DSM-IV). The ADHD subjects were at least 1.5 standard deviations above the mean on the Iowa Conners Teacher Rating Scale (CTRS) Inattention/Overactivity factor. ADHD subjects were obtained from a University private practice setting and were middle class in terms of socioeconomic and occupational status. Control subjects were children of both professional and clerical staff at the medical school. IQ and achievement testing were not obtained, but all subjects were fully literate in English, were attending regular schools, and did not require any special education or tutoring for educational deficiencies. Exclusionary criteria were the presence of any comorbid anxiety, depressive, conduct or psychotic disorder.

All of the ADHD subjects were positive responders to stimulant treatment and had been on stimulant treatment for at least one year, but were kept off medication for at least 24 hours prior to testing. The controls did not meet criteria for any other psychiatric disorder on the DISC evaluation and were in regular education classes. Written informed consent was obtained from all parents and all children assented to the study. All procedures were carried out according to the Declaration of Helsinki (British Medical Journal, 302: 1194, 1991), and approved by the Institutional Review Board of the University of Texas Health Science Center in San Antonio.

Subjects in the present report are from a previously published study that focused on a right inferior frontal N200 abnormality in ADHD (Pliszka et al., 2000).

Task

ERP Study. Each child performed the Stop Signal Task (Logan et al., 1984). As implemented here, the letters A or B (GO stimuli) appeared at the center of the screen for 150 msec, immediately above a fixation point. Intertrial interval varied randomly between 1.5 and 1.8 sec (mean 1.65 sec). The child pressed one button for the letter A, and a second button for the B, using the index finger of each hand. On 25% of the trials, the GO stimulus was followed by the STOP signal (the letter S), appearing for 150 msec just below fixation. The interval between GO and STOP signal (STOP signal interval) varied randomly between 200 and 600 msec (modified from run to run as noted below). The child was instructed *not* to press the button on these trials with STOP signals. When the STOP signal occurs soon after the GO Signal, it is fairly easy for the subject to inhibit the response, and the percentage of failed inhibitions is relatively low. In contrast, when the STOP signal occurs at a longer interval after the GO signal, the subject fails more often to inhibit (Schachar and Logan, 1990). Probabilities of Inhibition [P(I)], slopes and Stop Signal Reaction Time (SSRT) can then be calculated for each of the four 100 msec Stop Signal Intervals (200-300, 300-400, etc.). SSRT (the time to inhibit a response) is calculated by identifying the response in the ranked RT distribution (responses to GO trials) that corresponds to 100 minus the Probability of Inhibition (Pliszka et al., 1997; Schachar and Logan 1990).

In the present ERP study, the level of difficulty of the inhibition process for each run was adjusted according to the global mean reaction time (GMRT) to the GO stimuli in the preceding run. If the GMRT to the GO trials (i.e., those not followed by STOP signals) in the prior block was slower than 600 msec, the difference relative to 600 msec was added to all STOP signal SOAs in the following block. This prevented the child from systematically "beating the S" by slowing down his RT until he was sure there was no STOP-Signal. There were a total of 10 runs, separated by short rest periods. Each run lasted about 3 minutes and contained 144 GO signals along with 48 STOP signal trials (12 at each of the 4 stop signal delays. The present paper is a further analysis of ERP data previously collected in the same subjects during the SST. The published report focused on a right inferior frontal N200 abnormality in ADHD (Pliszka et al., 2000).

ERP Methods

Brain electrical activity was recorded using a customized cap with an array of 64 equally spaced electrodes (Electrocap Inc., Eaton, OH) referenced to the right mastoid. Recording settings were: bandpass = 0.01-100 Hz, gain = 10,000, sampling rate = 400 Hz, impedances < 5k (SA amplifiers, San Diego, CA). Trials with eye movement artifacts were rejected off-line. ERPs were selectively averaged for the following trial types: GO (A or B not followed by a STOP signal, 75% of the trials), Successful Inhibitions (SI; A or B followed by a STOP signal, with response correctly withdrawn), and Failed Inhibitions (FI; A or B

TABLE I
Performance on Stop Signal Task ADHD vs. Controls

	ADHD	Control	p
No.	10	10	
Age	11.0 yrs (1.2)	11.3 yrs (0.9)	.53
Iowa CTRS			
Inattention	2.0 (0.7)	0.3 (0.2)	.001
Aggression	0.6 (0.6)	0.1 (0.3)	.001
Accuracy on GO task	85.7% (7.1)	96.0% (3.5)	.001
Grand Mean RT	625 ms (140)	679 ms (114)	.352
Mean SD of RT	197 ms (43)	152 ms (17)	.009
Mean SOA Adjustment after each block	78.3 ms (90.6)	103.3 ms (93.7)	.55
SSRT	428 ms (155)	337 ms (73)	.12
Slope	0.70 (.84)	2.0 (.40)	.001

Means (Standard Deviations) of demographic variables and performance measures in the Stop Signal Task in the ADHD and control group. Data previously published in Pliszka et al., 2000.

followed by a STOP signal, incorrect button press). ERPs were averaged 4000 msec post-stimulus, with a 400 msec pre-stimulus baseline and digitally filtered with a non-causal, zero-phase running average filter of 9 points. ERPs to the SI and FI trials were analyzed time-locked to the onset of the STOP signal.

After artifact rejection, subject averages among healthy children contained an average of 154 trials for the Successful Inhibition trials (range 75 to 255), and an average of 118 trials for the Failed Inhibition trials (range 50 to 220). Subject averages in the ADHD group contained an average of 85 trials for Successful Inhibition trials (range 30 to 145), and an average of 170 trials for the Failed Inhibition trials (range 73 to 248). In order to correct for the expected different proportion of successful and failed inhibition trials in the two groups as a function of STOP signal interval, ERP subject averages were calculated after equally weighting the subaverages for each of the four STOP signal intervals (for more detail, see Pliszka et al., 2000). To compute the ERN, ERPs to GO trials were selectively averaged for correct responses (Hits) and incorrect responses (Errors), time-locked to the latency of the button press. After artifact rejection, subject averages for the Incorrect responses in the healthy control group included an average of 64 trials (4.5% of the Go stimuli; range 32 to 90). In the ADHD group, subject averages included an average of 325 trials (17% of the Go stimuli; range 75 to 552). Individual subjects' ERPs were then grand-averaged for each trial type for the ADHD and control groups.

Topographic maps of the ERP scalp distributions for the different trial types and group difference waves were created using the spherical spline method (Perrin et al., 1989).

In order to examine group differences in the selected effects at specific scalp sites, including possible differences in scalp topography, mean voltage amplitudes in the P3a and ERN latency windows for each subject underwent a normalization procedure with the square root of the mean of squares method (McCarthy and Wood, 1985). Normalized mean voltage values were entered in repeated-measures ANOVAs. P-value was set at .05, and degrees of freedom were corrected for deviations from sphericity with the Greenhouse-Geisser epsilon method.

Results

Behavioral Results

Characteristics of the subjects and the performance of the groups on the Stop Signal Task are shown in Table I. Paired t-tests were employed for the following behavioral parameters: global mean reaction time (GMRT), reaction time variability and discrimination accuracy in the GO task, STOP signal reaction time (SSRT), and Percent Failed Inhibitions for each STOP signal interval.

The ADHD group was rated as much more inattentive and overactive ($t = 7.5$, $df = 18$, $p < .001$) and oppositional ($t = 2.4$, $df = 18$, $p < .001$) on the Iowa Conners Teacher Rating Scale. The ADHD group was less accurate on the GO Task ($t = 4.1$, $df = 18$, $p < .01$) and committed more omission errors (i.e., missed responses to GO trials) [$F (1, 18) = 5.8$, $p < .03$], and while the groups were not different in the GMRT, the ADHD subjects were more variable in reaction time ($t = 3.1$, $df = 18$, $p < .01$). There was a non-significant trend toward a slower SSRT in the ADHD groups. As expected (Pliszka et al., 1997), however, the ADHD subjects had a flatter response-inhibition slope than the control group ($t = 4.5$, $df = 18$, $p < .01$) and a smaller overall percentage of Successful Inhibitions ($t = 4.9$ $df = 18$, $p < .04$) (see Figure 2).

ERP Results

Three effects were evident from the inspection of the group grand-averages and topographic maps (controls and ADHD), and the ADHD minus

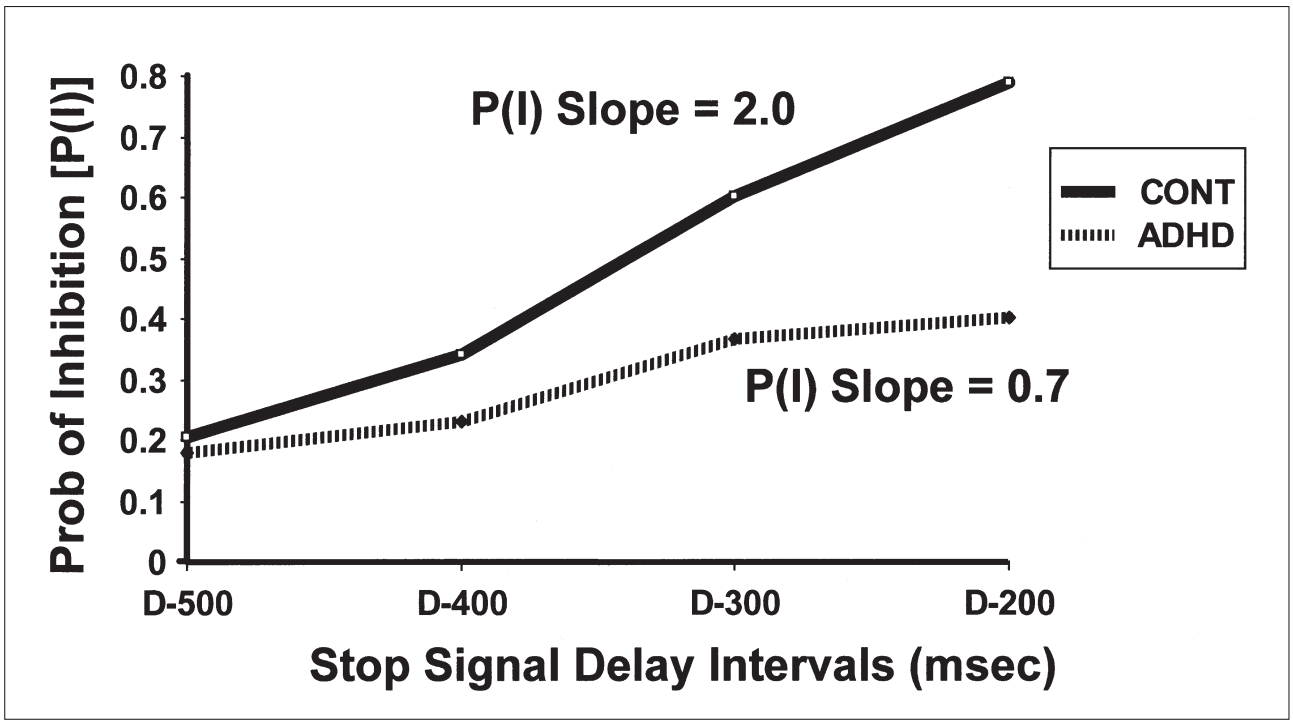

Fig. 2 – *Percent Failed Inhibitions in the ADHD and Control groups as a function of GO-STOP delay interval. Note steeper slope in the Control group.*

Control difference waves. First, the ERP to the Stop Signal in control children (for both SI and FI trials) showed a sharp negative wave peaking at 200 msec over right inferior frontal scalp (N200), which was markedly reduced in ADHD children (see Figure 1). This finding was described in a previous report (Pliszka et al., 2000). Second, the ERP to the Stop Signal in control children showed a large amplitude positive wave peaking at 320 msec for Successful Inhibitions only, with a medial anterior frontal distribution (P3a), which was also markedly reduced in ADHD children (see Figure 3). A latency window centered over the grand-average P3a (280-350 msec) was chosen to study this effect. Third, in the control group the ERPs to GO Errors (FI trails, time-locked to the button press) showed a sharp negative peak which was absent in the ERP to GO Hits (30-80 msec, peak at 65 msec after the button press), with a focal distribution over midline anterior frontal scalp. This typical error-related negativity (ERN) was also markedly reduced in the ADHD group (see Figure 4).

For the P3a analysis (280-350 msec), a set of four left-right anterior (site 9-10, 11-12, 19-20, and 13-14) and four posterior electrode sites (site 49-50, 47-48, 57-58, 45-46), close to the scalp midline, were chosen. (see Figure 3 bottom right for scalp locations). In order to assess anterior-posterior, and left-right differences in this activity, four regions of interest (ROIs) were selected (two per hemisphere) by collapsing together mean voltage amplitudes over these sets of four adjacent electrode sites. These ROIs included identical left and right medial anterior (frontal), and medial posterior (parietal) scalp sites. A mixed-design repeated measures ANOVA was carried out with factors being Group (ADHD vs. Controls), Anterior-Posterior Topography (Ant vs. Post ROI), and Hemisphere (Left vs. Right). Analyses were carried out separately for SI and FI trials.

The ERN analysis (30-80 msec) was conducted on a subset of six midline scalp sites, in anterior-posterior order (sites 2, 3, 4, 38, 37 and 36; see Figure 4 bottom right for scalp locations), with factors being group (ADHD vs. Controls) and Trial Type (Errors vs. Hits). This was followed by individual analyses within each group separately.

Medial Anterior P3a (280-350 msec)

Following the N200, the ERP to successful inhibition (SI) trials in the control children showed a large amplitude positive wave peaking around 320 msec post-Stop-Signal (P3a), which was much less pronounced for failed inhibition trials (FI). This P3a to SI trials was markedly reduced in the ADHD children. The group difference had a focal distribution over medial anterior scalp, with a maximum over the right hemisphere (see Figure 3).

SI Trials. The P3a amplitude group difference in the ERPs to the Stop Signals for Successful Inhibitions trials observed in the waveforms and topographical maps was corroborated by a significant interaction involving Group and Anterior-Posterior Topography, $F(1, 18) = 6.25$, $p = 0.02$. A significant group difference was exclusively present over the anterior medial scalp region: P3a amplitudes were significantly smaller

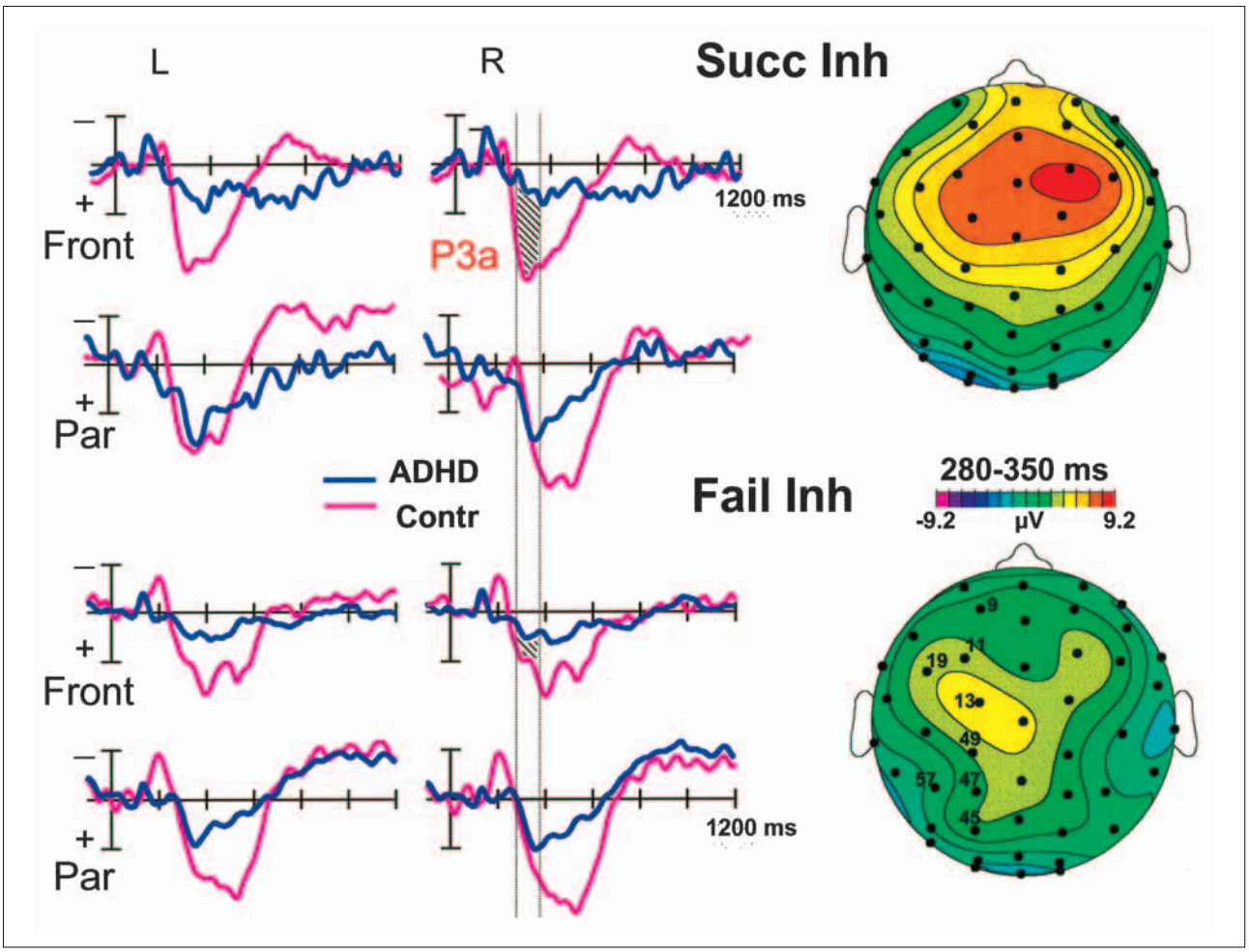

Fig. 3 – *P3a to the Stop Signal (280-350 ms). Left: Grand average ERPs for Control (purple) and ADHD (blue) for Successful Inhibition (Succ Inh, top) and Failed Inhibition trials (Fail Inh, bottom), for anterior medial (frontal) and posterior medial (parietal) scalp regions. L = left; R = right. Zero point is the Stop signal onset. Right: Topographic maps of the ERP difference wave for Controls minus ADHD for Successful Inhibition trials (Succ Inh, top) and Failed Inhibition trials (Fail Inh, bottom). Note the focal distribution of this difference wave over anterior medial scalp (slightly to the right) occurring for Succ Inh only. The topographic map on the bottom right shows the anterior and posterior sites included in the analysis of the P3a (left side only).*

over this scalp area in the ADHD children relative to control children, whereas they were of similar amplitude over the medial posterior region (see Figure 3). Although the effect was maximal over right medial frontal scalp (site 12), there were no significant interactions involving group and hemisphere (for all, $F < 1$, n.s.).

FI Trials. In contrast to the SI trials, P3a amplitudes to the Stop Signals in case of Failed Inhibitions were not statistically dissimilar as a function of Group and Anterior-Posterior distribution, Group X AP factor, $F (1, 18) = 0.9$, $p = 0.79$, n.s. No other main effect or interaction approached significance (for all, $F < 1.4$, n.s.).

P3a correlation with Performance. In order to test the hypothesis that the P3a amplitude reduction is related to a failure in response inhibition, simple correlations were performed between individual behavioral parameters in the Stop Signal task and each child's mean amplitude of the right frontal P3a for the Successful Inhibition Trials. P3a amplitudes over right medial anterior scalp showed a significant positive correlation with Percent of Successful Inhibitions, significant in the ADHD group only, $r = .62$, $p < .02$ (for the control group, $r = .02$, n.s.).

ERP changes to Errors vs. Hits (ERN). In response to the GO stimuli in the control children, the ERP to the errors (FI trials) was more negative (30-80 msec post-button-press) than the ERP to the hits (trials with no Stop signal), with a minimum over medial frontal scalp (site 3 or FCz) and a focal scalp distribution over medial anterior frontal scalp in the Current Density maps (see Figure 4 top right). In contrast, no appreciable ERN effect was evident in the grandaverage waveforms for the ADHD group, and in the correspondent Scalp Current Density maps (see Figure 4 bottom).

Control children. The mean amplitude of the ERP to the Errors was significantly more negative than the ERP to the Hits. The strongest effect was over anterior medial frontal scalp, $F (1, 9) = 5.8$, $p < 0.04$, and frontocentral scalp, $F (1, 9) = 5.2$, $p < 0.05$, consistent with a generator in anterior cingulate cortex (see scalp current density map in Figure 3 top right). No differences were present at posterior scalp locations.

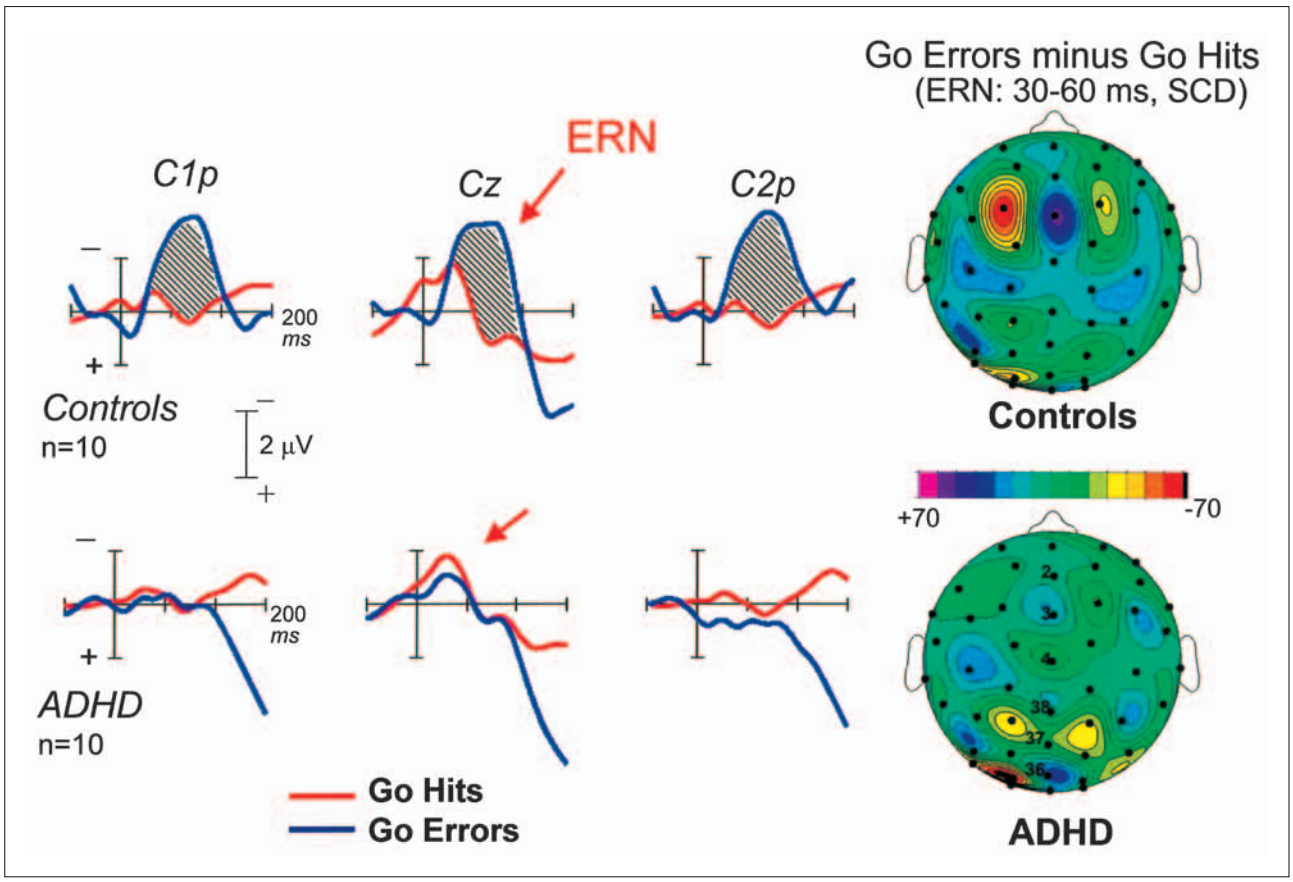

Fig. 4 – *ERPs to Errors (Failed inhibition trials) and Hits (Go trials), timelocked to the button press Left: Grand average ERPs for Controls (top) and ADHD (bottom) for Errors (blue) and Hits (red) over medial central left (C1p or site 13), midline (Cz or site 4) and right scalp sites (C2p or site 14). Zero point is the onset of the motor response. Shaded areas show the difference between Errors and Hits in the Control group (ERN), and its lack in the ADHD group. Right: Topographic maps of the Scalp Current Densities for the Error-minus-Hit difference wave (ERN) for Controls (top) and ADHD (bottom), from 30-60 ms post-motor response. Note the focal distribution of the Scalp Current Densities (SCD) over anterior medial scalp in the control group, and its absence in the ADHD group. The topographic map on the bottom right shows the midline sites included in the analysis of the ERN.*

ADHD children. In contrast to the control children, no significant ERN effect was present in the ADHD group at any scalp location. In particular, no effect was present over anterior frontal scalp, $F(1, 9) = 0.19$, n.s, as reflected by the lack of focal anterior activity in the Scalp Current Density maps.

ADHD vs. Control children. A global ANOVA with group as a factor showed a significant interaction of Group X Trial Type, $F(1, 18) = 4.7$, $p < .05$. No interactions with scalp site approached significance. The greatest group difference was present at the midline frontocentral scalp site (site 3 or FCz), $F(1, 18) = 5.3$, $p < .03$).

Discussion

The present ERP study describes two important findings related to inhibitory control and error processing in ADHD children during the Stop Signal Task. First, it identifies the timing of a processing component associated with successful inhibitory control in healthy children (the P3a), and its abnormal reduction in ADHD children. Second, it reports abnormally reduced amplitudes of the Error-Related Negativity (ERN) in ADHD children relative to healthy children, demonstrating a functional deficit in error processing in ADHD. The scalp topography (midline frontal) of both ERP effects suggests that they may both arise from midline frontal structures (the dACC in particular), and their abnormal reduction in ADHD children may suggest a global deficit in cognitive control operations supported by such structures.

P3a (280-320 msec)

Processing of Successful Inhibition trials was accompanied by a greater amplitude P3 wave (P3a) than processing of Failed Inhibition trials. Such activity was significantly reduced in the ADHD group with a focal group difference centered over medial anterior frontal scalp, greater over the right hemisphere and consistent with a possible dipole source in right dorsal ACC. Moreover, P3a amplitude to Successful Inhibition trials in the ADHD group correlated significantly with the percent of successful inhibitions in their performance data.

The greater amplitude of the P3a wave in control children appears to reflect the more efficient monitoring or successful implementation of the process of response inhibition, with the marked reduction in amplitude of ADHD children likely representing a deficit in this inhibitory process. This decreased brain activity is associated with the abnormal behavioral performance in the ADHD children, as indexed by the abnormal slope function in the Stop signal Task, and further supported by the significant correlation between P3a amplitude and behavioral indices of response inhibition in the ADHD group. This is consistent with a study reporting a significant correlation between children's performance in a difficult visual search task and the volume of the right dACC (Casey et al., 1997c). In the present study, the lack of a significant correlation between P3a amplitude and behavioral measures in the control group may be explained by less variability in P3a amplitudes in this group.

These combined findings, along with the midline frontal distribution of the effects, seem to implicate midline frontal structures in response inhibition and its impairment in ADHD children. This conclusion is supported by the findings of abnormally reduced BOLD fMRI activity in dACC in block-design fMRI studies during the Stop Signal Task and the Counting Stroop in ADHD subjects (Rubia et al., 1999; Bush et al., 1999) as well as the localization of fMRI activity in healthy children and adults during Go/NoGo tasks (Casey et al., 1997a). Dipole source analysis was not carried out in the present study, and fMRI data in the same subjects were not available. Therefore, the localization of the present ERP effects to dACC should be interpreted with caution.

P3a in Earlier Studies

ERP studies of visual or auditory oddball tasks have identified two P300 subcomponents, the P3a and the P3b. The P3b is evoked by the presentation of task-relevant infrequent targets. This component is largest over posterior (parietal) scalp. The P3a is an earlier latency component typically evoked by infrequent distracter or novel stimuli, which has a more anterior scalp distribution, and peak amplitude over frontal and central scalp regions (Hillyard and Kutas, 1983, for a review). The medial wall of the frontal lobe, including the anterior cingulate cortex, has been implicated as contributing substantially to the generation of the P3a to rare distracters by studies using intracortical recordings in epileptic patients (Brazdil et al., 1999; Baudena et al., 1995). Ebmeir et al. (1995) measured simultaneously brain metabolism with SPECT and electrical activity with scalp EEG in healthy subjects during auditory oddball tasks. They found that the amplitude of the P3a to novel distracters correlated positively with tracer uptake in anterior cingulate cortex. Finally, recent event-related fMRI studies in healthy controls during oddball tasks with infrequent targets and novel distracters have confirmed selective activation of anterior cingulate cortex to novel distracters is likely to be involved in the generation of P3a waves (Clark et al., 2000; Kiehl et al., 2001; Downar et al., 2002).

No studies have investigated P3a waves to novel stimuli in ADHD children. A published ERP auditory oddball study in healthy 9-year-old children with normal IQ found that distractible children compared to non-distractible children (defined by low scores on the Freedom from Distractibility factor[FFT]; Arithmetic and Digit Span of the Wechsler Intelligence Scale for Children-Revised [WISC-R]) produced a frontally distributed P3a to task-relevant targets, with no tendency to habituation (Kilpeläinen et al., 1999), as if such stimuli were novel or surprising. This finding of enhanced P3a activity in distractible children may seem at odds with the results of impaired P3a activity in ADHD children in the present study. However, the link between FFT performance and ADHD is very tenuous, since besides attention and concentration, FFT measures symbolic reasoning and manipulation of mathematical mental representations, and it does not tap directly into response inhibition. Furthermore, the children in Kilpeläinen et al. (1999) did not have a diagnosis of ADHD and were not tested for measures of Inattention/Overactivity (I/O), such as the CTRS I/O Factor).

Error Processing in ADHD

A second important and novel finding of this study is that ERP activity associated with error processing (the error related negativity or ERN), also known to have a significant contribution from generators in dACC (Kiehl et al., 2000; Gehering et al., 2001; Bush et al., 2000; Liotti et al., 2001), was found to be markedly reduced in ADHD children relative to healthy children. This is, to our knowledge, the first report of impaired ERN activity in ADHD, suggesting that error processing (error detection and correction) in the dACC is impaired in this developmental disorder.

Similar midline frontal scalp distributions in the present study in both the monitoring of successful inhibition performance (P3a) and the monitoring of errors (ERN) are consistent with recent accounts of dACC function as involved both in conflict monitoring in selective attention (such as in the Stroop task) *and* in error processing, as indexed by the ERN (Botvinick 2000, 2001; Van Veen and Carter, 2002; Liotti et al., 2001). In particular, ERP studies of conflict monitoring (Stroop Task, Eriksen flanker task) have reported co-localization of the error-related negativity and a negativity associated with cognitive conflict (both distributed over

midline frontal scalp, and source localized to the same dACC generators: Liotti et al., 2001; Van Veen and Carter, 2002). Such results are also consistent with recent event-related fMRI evidence showing that dACC activity is present both in response to Go and to NoGo stimuli (Liddle et al., 2001; Garavan et al., 2002).

Functional Role of Right Inferior PFC and Midline Frontal Cortex during Inhibitory Control

The use of high-density ERPs in the present study provides unique clues about the timing and stage of information processing of the involvement of prefrontal regions during the unfolding of the Stop Signal Task. More specifically, ERPs to the onset of the Stop Signal showed a marked reduction of an earlier and more transient ERP component in the ADHD group, the N200, with a focal distribution on the right inferior frontal scalp of the group difference effect (Pliszka et al., 2000) (see Figure 1). Such localization is consistent with the recent fMRI and lesion-correlation findings in tasks of inhibitory control (Garavan et al., 1999; 2002, Rubia et al., 1999, Aron et al., 2003). Importantly, N200 activity evoked by the Stop Signal had similar amplitude for Successful and Failed Inhibitions in the healthy boys, and both were reduced by the same extent in the ADHD group (Pliszka et al., 2000) (Figure 2). This is consistent with a functional interpretation of the N200 as a 'red flag' (Falkenstein et al., 1999) triggering the initiation of the inhibitory process, independent of its outcome. This right frontal 'braking mechanism' would operate in a similar way to the use of brakes in a vehicle – faced with a sudden obstacle in our path, we would 'hit the brakes' whether or not we can successfully stop the car in time.

Later in the processing, the ERP to the Stop Signal showed a marked reduction in the ADHD group of a slow positive ERP wave, the P3a, with a substantially different focal distribution over right medial frontal scalp. Although no source analysis was performed in this study, and fMRI data were not acquired, indirect support of the localization of this effect to dACC comes from the results of recent fMRI studies in ADHD during the Stop Signal Task (Rubia et al., 1999) and the Counting Stroop task (Bush et al., 1999). At variance with the earlier N200 effect, the P3a effect showed selectivity for the Successful Inhibition trials, suggesting that it may index a later stage in the inhibitory process, such as monitoring of its successful implementation.

The results of this study are consistent with the notion that a distributed network, including right middle lateral prefrontal cortex and right midline frontal structures (e.g., dACC), is involved in inhibitory control as tapped by the Stop Signal Task. Based on the timing and scalp distributions of our ERP effects, right lateral prefrontal cortex appears to be crucial for the initiation of response inhibition by triggering the inhibitory process, consistent with its previously reported more general role in other inhibitory control tasks (Go/NoGo, Wisconsin card-sorting task, etc). In contrast, dorsal ACC appears to be involved in monitoring processes during inhibitory control, including both monitoring of the successful outcome of the inhibitory process, and in monitoring errors in response to the Go stimuli. This view of the functional parcellation of lateral PFC and dACC activity is consistent with one proposed by a recent er-fMRI study during a Go/NoGo task (Liddle et al., 2001). Once again, the localization of the present effects should be interpreted with caution, given the lack of fMRI data in the same subjects and task.

Error Processing in ADHD

The ERP to Errors (Failed-inhibition trials) and to Hits (Go trials) showed a striking reduction of the Error Related Negativity in the ADHD group. This difference wave also possessed a very focal medial anterior distribution in the normal subjects, consistent with previous findings indicating that it likely originates from the dorsal Anterior Cingulate (Liddle et al., 2001). This finding is consistent with impaired error monitoring (error detection and correction) in ADHD.

A functional abnormality in midline frontal structures (dACC in particular) in ADHD children would account for both impaired monitoring of successful (correct) inhibitions, and impaired monitoring of errors, consistent with current accounts of the function role of dACC in cognitive control and action monitoring (Botvinick et al., 1999; 2001; Gehring and Fencsik, 2001).

Caveats and Current Directions

The present study should be considered preliminary, given the small sample size of the two groups and the lack of test-retest or split-half reliability data. The proposed localizations of the ERP effects should be interpreted with caution, given the lack of ERP source dipole modeling, and the absence of converging data from fMRI in this sample of children and this version of the SST.

The effects of acute and chronic stimulant treatment on the ERP findings were not examined in this pilot study (see below). All the ADHD children were on chronic treatment (> 1 year), stimulant medication, suspended 24 hr before the study. Acute methylphenidate interruption has been found to cause a rebound of activity in motor/premotor cortical areas, possibly a direct effect of dopamine on motor inhibition mechanisms (Bell et al., 1983). In addition, a recent SPECT study showed that acute suspension

of methylphenidate (MPH) treatment in chronically treated ADHD boys (comparable to the subjects in the present study) resulted in an increase in anterior cingulate activity during a Go/NoGo task, compared to similar ADHD boys without MPH suspension (Langleben et al., 2002). No healthy subjects were included in that study, making the comparison with the present findings difficult. Whereas further studies are necessary to explore the influence of acute and chronic stimulant treatment in ADHD, it is worth pointing out that MPH withdrawal cannot explain our P3a and ERN group differences (abnormal reductions), because if anything the possible influence of acute MPH interruption would have resulted in an inverse sign influence on functional indices of dACC function, i.e., reducing rather than increasing the size of the ERP effects.

A potential confound of the P3a findings is that SI trials include Successful inhibitions in response to the STOP signal as well as omissions (unattended STOP signals due to lapses in concentration). In this paradigm an independent measure of omissions was available from the GO trials. ADHD children did in fact have significantly more omissions on such trials than the healthy control group (see Table I). It is unlikely however that the presence of omissions among the SI trials can account for the P3a group difference. In a different ERP study of the SST in healthy adults (Schmajuk et al., submitted), we included a STOP-irrelevant condition, in which STOP signals were present but subjects were asked to not pay attention to them. The comparison of the STOP-relevant and STOP irrelevant conditions isolated a posterior N200 subcomponent with parietooccipital distribution, likely reflecting early sustained attention to the STOP signal (Schmajuk et al., submitted). Figure 2 shows that the amplitude of the N200 to the STOP signal over posterior scalp sites in the present study was of similar amplitude among the two groups, while it was the N200 amplitude over right inferior frontal scalp that showed a dramatic difference among the two groups, likely reflecting the selective impairment of an N200 subcomponent associated to response inhibition (Pliszka et al., 2000; Schmajuk et al., submitted). It is considered unlikely that a difference in omissions (due to lapses in concentration) among SI trials would affect the frontocentral P3a but not affect the posterior N200, more specifically linked to task relevance and early sensory attention.

Our group is currently carrying out a larger scale replication and extension of this pilot study, involving combined use of ERPs and fast rate event-related fMRI during the Stop Signal Task and the Stroop Task, neuropsychological evaluation, and MRI morphometry. Preliminary analysis of the fMRI data in the Stop Signal Task (12 healthy children, 10 ADHD) confirms robust activations of right middle and inferior frontal gyri and right dACC in the healthy group, and reduction such effects in the ADHD group (unpublished data, University of Texas Health Science Center at San Antonio). Issues addressed by the current project, are: a) The effect of acute or chronic stimulant treatment on the ERP abnormalities, by comparing previously stimulant treated to stimulant treatment naive ADHD children, and the effects of best dose acute methylphenidate treatment versus placebo; b) the specificity of the findings to ADHD, by testing a comparison group of children with another developmental condition, i.e., Reading Disorder; the effects of gender (boys or girls) and puberty (prepuberal versus postpuberal).

It is believed that a within-subject multimethodological approach combining neuropsychology and morphometric analysis to behavioral, electrophysiological, and neuroimaging measures of response inhibition will greatly improve our understanding of the brain-behaviour relationships in ADHD.

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