Response Inhibition in Preschoolers at Familial Risk for Attention Deficit Hyperactivity Disorder: A Behavioral and Electrophysiological Stop-Signal Study

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Children participating in the Ben-Gurion Infant Development Study were assessed with a dynamic-tracking version of the stop-signal task at the age of 5 years. The sample consisted of 60 males. Stop-signal reaction time (SSRT) was correlated with concurrent ratings of the child’s attention deficit hyperactivity disorder (ADHD) symptoms. Paternal symptoms measured in the child’s early infancy predicted the child’s performance in the stop-signal task: Paternal inattentiveness predicted SSRT, whereas hyperactivity predicted error proportion. Maternal symptoms were not correlated with the performance of the child in the task. A subsample of children, who were tested while electrophysiological brain activity was measured, showed that having higher ADHD symptomatology, especially hyperactivity, correlated with less activity in the brain areas that are usually recruited by children for successful inhibition.

This study focuses on identifying an early marker in the developmental pathways of inhibitory control deficits in attention deficit hyperactivity disorder (ADHD) and the brain circuitry implicated in this deficit. The search for endophenotypes entails looking for quantitative indices of disease liability that predict the risk of ADHD. The motivation for looking for such markers is that symptom-based diagnostic classification systems have failed to provide a clear map between risk factors, such as susceptibility genes and behavioral outcomes (Doyle et al., 2005). Inhibitory control has been suggested to be an endophenotype of the disorder (Castellanos & Tannock, 2002) and could be such a marker.

Inhibitory Control and Its Development

Inhibition is an executive function that reflects the ability to deliberately inhibit dominant or automatic responses (Miyake et al., 2000). Although the requirement to suppress a prepotent response may be present in multiple task contexts, such as task switching, Stroop interference, and so forth, it is most clearly measured by Go-NoGo and stop-signal paradigms (Aron & Poldrack, 2005). In the Go-NoGo task, participants are required to respond only to the appearance of the go stimuli and to inhibit response to the no-go stimulus. The stop-signal task is a specific type of Go-NoGo task designed to measure the most challenging form of response inhibition, namely, stopping a response that has already been prepared for execution (Logan, 1994). The idea in the stop-signal task is that while the participant is responding to the go stimulus (usually within a discrimination task), a stop signal appears in a small proportion of the trials (usually 25%-30%) at an unpredictable delay after the go stimulus. The stop signal tells the subject to withhold the response to the go stimulus. When the stop signal appears shortly after the go stimulus, the task is relatively easy. In contrast, when the stop signal appears after a long delay from the appearance of the go stimulus (i.e., close to the time of response), subjects often fail to inhibit their response, which has probably already been “launched” (Schachar & Logan, 1990). In this task, it is possible to calculate stop-signal reaction times (SSRT) and inhibition functions (the percentage of failed inhibitions as a function of the go-stop delay interval; Schachar & Logan, 1990). An advanced
and efficient strategy for setting the delays between the go and the stop signals is to dynamically track the participant’s performance (Osman, Kornblum, & Meyer, 1986; Schachar & Logan, 1990). In such a tracking paradigm, the finishing time of the stopping process (SSRT) is estimated by employing the formula SSRT = mean go reaction time – median delay.

The development of response inhibition has been studied across the life span with the stop-signal task, from 7 to 81 years of age (Schachar & Logan, 1990; Williams, Ponesse, Logan, & Tannok, 1999). Results of these studies indicate that there is an improvement in inhibitory control during childhood (shortening of the SSRT with age) and then some deterioration after middle adulthood. The performance of 6-year-old children in these studies was found to be unreliable. Still, there have been a few successful attempts to adapt the stop-signal task for preschoolers, such as the research conducted by Carver, Livesey, and Charles (2001) and Tillman, Thorell, Brocki, and Bohlin (2008). We have developed a version of a dynamic-tracking stop-signal paradigm, based on a color-choice go task that is suitable for testing preschoolers. Preschool age is of special interest, as this age seems to be a turning point in the development of inhibitory control and self-regulation (Berger, 2011). Around the age of 4 years, there is a major increase in a child’s ability to withhold a response (Carlson & Moses, 2001; Diamond & Taylor, 1996). There is also a substantial improvement in conflict resolution at this age including stimulus selection, for example, Zelazo’s Card Sorting Task (Zelazo & Jacques, 1996); response selection, for example, the Day-Night Stroop Task (Gerstadt, Hong, & Diamond, 1994); and inhibition of a prepotent response, for example, the Spatial-Conflict Task (Berger, Jones, Rothbart, & Posner, 2000). In a pilot study (Berger & Alygon, 2004), our staircase dynamic-tracking stop-signal paradigm was tested on a sample of 149 children in preschool, first, and second grades (67 males). Results indicate that children as young as 54 months of age are able to perform the stop-signal paradigm provided the task is adapted to their capabilities. As pointed out by Carter et al. (2003), the advantages of a tracking paradigm such as ours are (a) the initial value of the delay is not arbitrarily set, but instead is set proportionally to the mean go reaction time of the individual participant; (b) delays are not preset to fixed values, but instead are dynamically changed by tracking the participant’s performance; and (c) since this paradigm requires a relatively small number of trials, it is suitable for studying special populations, such as children at risk for ADHD, as in the current study.

At the brain activity level, studies in adults using event-related potential (ERP) methodology—a technique based on an electroencephalogram (EEG) that possesses a very high temporal resolution (milliseconds) and can identify the timing of brain processes during cognitive tasks—relate the inhibition process to the time window around 200 ms after the presentation of the stop or no-go stimulus. The inhibition process is usually reflected in the N2 component, which has a frontal or parietal distribution (i.e., this wave form appears at electrodes located in frontal areas of the scalp; Falkenstein, Hoormann, & Hohnbein, 1999; Pliszka, Liotti, & Woldorff, 2000), which also reflects attentional and categorization processes (for review of the N2 component, see Folstein & Petten, 2008). As for the neuroanatomical bases of inhibitory control processes, studies with primates, as well as imaging studies in human adults, indicate that the prefrontal cortex (PFC), especially the right inferior frontal cortex (IFC), is active in tasks such as the Go-NoGo and stop-signal paradigms and seems to play a critical role in response inhibition (Aron & Poldrack, 2005).

However, interesting developmental differences are found when comparing children’s brain activity that is related to successful inhibition with the results found in studies with adults. Most of the developmental imaging studies tend to support the idea that children recruit larger, more diffuse prefrontal regions, whereas adults show much more focal activation in the critical right prefrontal regions, which seem to specialize in response inhibition (Casey, Galvan, & Hare, 2005). This developmental process is also reflected at the ERP level, usually as an age-progressive decrease in amplitude and latency of the N2, although there have been inconsistent findings in this regard (see a more detailed review of this literature in Berger, 2011).

Moreover, at least one study suggests that children may actually recruit completely different circuitry than adults when trying to inhibit a response. Bunge, Dudukovic, Thomason, Vaidya, and Gabrieli (2002) showed, with event-related fMRI, that the differences in brain activation when trying to inhibit a response for 8- to 12-year-old children and adults involved the hemisphere where interference suppression occurred. Specifically, effective interference suppression in adults was associated with right PFC activation, whereas effective interference suppression in children was associated with prefrontal activation in the left insula and inferior frontal gyrus, which are brain regions...
related to language. A plausible explanation of this activation was that adults could recruit the specialized required circuitry, whereas children may have used verbal aid for succeeding in the task.

**ADHD and Inhibitory Control**

ADHD is one of the most common childhood psychiatric disorders, characterized by chronic and age-inappropriate symptoms of impulsivity, hyperactivity, and inattention (American Psychiatric Association, 1994). The behavioral deficits that are characteristic of ADHD usually arise relatively early in childhood, typically before the age of 7 years and are fairly persistent (Barkley, 1997). One of the most well-documented deficits seen in children with ADHD is their difficulty with inhibitory control (Nigg, 2001), and this deficit is considered an important factor in the etiology of this disorder (Aron & Poldrack, 2005; Willcut, Doyle, Nigg, Farace, & Pennington, 2005).

One of the best established measurements of this impairment is the stop-signal task (Stevens, Quittner, Zuckerman, & Moore, 2002). The inhibition slopes obtained from children with ADHD are flatter, reflecting a less effective inhibition process in this population (Schachar & Logan, 1990) and their SSRTs are longer than those of control subjects (Pliszka et al., 2000; Schachar et al., 2004); to inhibit a response, ADHD subjects need to see the stop signal soon after the appearance of the go stimulus. This finding has been reconfirmed in a meta-analysis of 33 studies (Lijffijt, Kenemans, & van Engeland, 2005). Moreover, the SSRT of children with ADHD has been found to correlate with their ratings of hyperactivity (Pliszka, Borcherding, Spratley, Leon, & Irick, 1997). The only other study that has used the stop-signal task with children of this age was developed by Tillman et al. (2008). Tillman et al. tested a large sample of 4- to 12-year-old children and found that the SSRT and inhibition ratio were significantly related to teacher ratings of inattention (Tillman et al., 2008) as well as to performance on other tasks tapping inhibition, such as the Day-Night Stroop-like Task (Gerstadt et al., 1994).

The deficits in inhibitory control seen in children with ADHD are consistent with evidence for structural and functional differences between these children and controls in brain circuits that are involved in self-control (Casey, 2001). This circuitry involves brain structures such as the anterior cingulate cortex, areas of the PFC, (specifically the right IFC; Aron & Poldrack, 2005), the basal ganglia, and the cerebellum (Casey, Nigg, & Durston, 2007). Moreover, the deficits in the performance of children with ADHD in the stop-signal task have been found to be affected and, at least partially, corrected by stimulant medication such as methyl-phenidate (Tannock, Schachar, & Logan, 1995). Furthermore, ERP studies have demonstrated that the behavioral abnormalities of children with ADHD in the stop-signal task are accompanied by deviations in electrophysiological measures, such as N2 latency and amplitude (Dimoska, Johnstone, Barry, & Clarke, 2003; Pliszka et al., 1997).

Along with the literature suggesting inhibitory control deficits in children with ADHD, there is an expanding body of findings that show increased reaction time (RT) variability in this population (Kuntsi & Klein, 2012). The highly variable response times of subjects with ADHD in the go task led to questions regarding the extent to which longer SSRT reflects deficits in the postulated inhibitory process (Castellanos & Tannock, 2002).

ADHD is considered a developmental disorder; however, its developmental course and the pathways leading to it are relatively uninvestigated. Specifically, the developmental pathways leading to inhibitory control deficits of ADHD are unknown. Since the diagnosis of ADHD commonly occurs only in preschool or elementary school, a search for early markers of the disorder requires a longitudinal research paradigm. A prospective “high-risk research strategy” is of particular value in identifying the developmental course of psychiatric disorders because it targets, as the subject population, individuals at high risk for the disorder and then follows them over time to identify possible markers of the disorder. For disorders that show strong genetic heritability, such as ADHD, the individuals identified as high risk are usually first-degree relatives of patients with the disorder. Indeed, first-degree relatives of children with ADHD are 7.6 times more likely to have the disorder than are relatives of normally developing children (Biederman et al., 1992). Furthermore, 60% of children having a parent with ADHD are likely to receive a childhood diagnosis of ADHD (Biederman et al., 1995). The high heritability estimates (75%–90%) for ADHD in twin studies also support a strong genetic contribution (Goodman & Stevenson, 1989), although the expression of the disorder is most likely the result of the combined impact of genetic and environmental or epigenetic factors (Taylor, 1999). Indeed, environmental factors, such as family relationships, parent-child interaction, and family adversity, seem to
contribute to the development and severity of the disorder (Biederman et al., 1995; Cunningham & Barkley, 1979). In this sense, parental ADHD might provide a “familial risk” both in terms of genetic heritage and the rearing environment in which the child develops.

Using a prospective longitudinal high-risk paradigm, the Ben-Gurion Infant Development Study (BIDS) has been following, since birth, a sample of children at familial risk for ADHD. In this study, the risk for ADHD has been defined as the presence of ADHD symptoms in fathers. We assessed this sample periodically during home and lab visits. Our measures included parent-report questionnaires as well as systematic behavioral laboratory measures. The BIDS sample provides a unique opportunity for tracing the risk for developing ADHD and looking for its developmental pathways.

The Present Study

In this study, we tested preschoolers at different risk levels for ADHD with our dynamic-tracking stop-signal paradigm and predicted their performance based on the prospective data within the BIDS longitudinal study. Overall, data were collected over a period of 5 years, beginning with the birth of the child.

The primary aim of the study was to test whether preschool children at familial risk for ADHD would show less inhibitory control. Specifically, we investigated whether ADHD risk defined by paternal symptoms could predict SSRT. We hypothesized that as early as preschool age, children with a familial risk for ADHD would display less inhibitory control, which would be reflected in longer SSRTs and lower inhibition ratios in the stop-signal task, and that this deficient performance in the stop-signal task would be related to the concurrent ADHD symptoms of the child. Moreover, we hypothesized that children at risk might also show higher RT variability. As mentioned, we also tested whether the ADHD risk effect on SSRT was beyond the effects of RT variability, which characterizes the disorder.

The second aim of this study was to identify electrophysiological processes that may mediate behavioral performance in a response inhibition task. We hypothesized that children at the age of 5 years who showed symptoms of ADHD would also show less efficiency in the ability to recruit the brain circuitry necessary for inhibitory control.

Method

Participants

The sample consisted of 5-year-old boys at familial risk for ADHD. Our sample was limited to boys because ADHD is more prevalent in boys than in girls, with a ratio of 3:1–9:1 (Barkley, 1990; Danc-kaerts & Taylor, 1995). In principle, our sample was chosen based on the fathers’ symptoms, although information on the mothers’ symptoms was also collected. There is evidence that children are more affected when the affected parent is of their gender (Minde et al., 2003). Moreover, exposure to paternal ADHD appears to be as important as exposure to maternal ADHD (Biederman, Faroane, & Monuteaux, 2002).

All children were from two-parent families who were either native-born Israelis or immigrants who had studied in Israel and spoke Hebrew. These boys have been followed longitudinally since birth and were enrolled in the Ben-Gurion Infant Development Study based on paternal ADHD symptomatology initially assessed at the birth of the child. Initial recruitment was done based on an ADHD symptoms questionnaire using a yes–no format that the father completed at the hospital at the time of his child’s birth (see Auerbach, Aztaba-Poria, Berger, & Landau, 2004). When the children in the study were between 2 and 6 months old, the parents underwent a psychiatric interview (see more details in Landau, Amiel-Laviad, Berger, Atzava-Poria, & Auerbach, 2009). In addition, both parents completed the Conners Adult ADHD Rating Scale (CAARS; Conners, Erhardt, & Sparrow, 1998), both about themselves and about their spouses. These questionnaires produced a continuum of risk scores that was used in this study. In other words, based on parental symptoms, our sample consisted of children ranging from very low risk to high risk of developing ADHD.

Between 2001 and 2003, all the children in BIDS, who had their fifth birthday between these years, were invited to participate in the stop-signal part of the study (a total of 60 children). These children were tested with the stop-signal task. Four of these children were excluded from any analysis because they failed to attend to task instruction as demonstrated in accuracy below chance on the simple color discrimination go task. Eighteen of these boys performed the stop-signal task in the ERP lab. For these 18 children, the full set of measures was available for analysis: parental symptoms, child’s symptoms, child behavioral performance in the
stop-signal task, and ERP data in the stop-signal task. Table 1 presents the background variables of the stop-signal behavioral and ERP samples in comparison to the entire BIDS sample. Our samples did not differ on any of these variables from the total BIDS sample; neither does it differ in the degree of risk for ADHD according to the fathers’ and mothers’ symptomatology.

**Stimuli and Apparatus**

*The stop-signal task.* This task was presented to the participants as a set of computerized games. Since children at this age get bored very quickly, the trials were divided into three different stories or games. All the games had the same basic structure, and the child was asked to discriminate between two stimuli according to their color. For example, in the apples game, the child was instructed to help Little Red Riding Hood sort apples for Grandma into the corresponding baskets, according to color. The constant stimuli on the screen consisted of two baskets, one red and one green (the position of the colors was counterbalanced across participants). The trial began with a fixation point, which was a flickering star at the center of the screen. Fixation ended when the experimenter clicked the mouse button. Then, either a green or a red apple, which was the go stimulus, appeared at the center of the screen. Choice reaction time and correctness of response were measured. The go signal remained on the screen until the child responded, or for a maximal exposure duration of 1500 ms. If the apple was then replaced by a worm, which was the stop signal, the child was instructed to refrain from responding; otherwise, “the worm would be able to eat the apples in the basket.” In 30% of the trials, the stop signal appeared (see schematic representation of go trials and stop trials in Panel A of Figure 1 and the stimuli corresponding to each of the different games in Panel B of Figure 1). Positive feedback was given to the child after each successful trial, which was either the correct choice in a go trial or the successful inhibition of response in a stop trial. The feedback was a cheerful positive sound lasting 600 ms. There were 60 trials per block (game): 42 go trials and 18 stop trials; the total number of trials per participant was 180 (126 go trials and 54 stop trials). Actual sizes of stimuli on the screen (in centimeters): flickering star 1.8 × 1.8; go signal (apple, flower, sheep) 2.7 × 2.6; stop signal (worm, mushroom, wolf) 3 × 3; constant container (basket, vase, barn) 4.2 × 4.4. The entire session lasted about 30 min. The games were programmed in E-Prime Studio version 1.1.4.1 (Psychology Software Tools, 1996–2002). We used a staircase dynamic-tracking paradigm in which the computer tracked the child’s performance and adjusted the delay between the beginning of the go and the beginning of the stop signal, accordingly. The algorithm tried to lock on the delay where the child succeeded in inhibiting 50% of the stop trials.

| Table 1: Background Variables of the Sample at Entrance to the Longitudinal Study |
|--------------------------------|--------------------------------|--------------------------------|
|                               | SS sample                      | ERP sample                      |
|                               | N = 60                          | N = 18                          |
| Mother’s age                  | 29.3 (5.0) year                 | 29.9 (4.7) year                 |
| Mother’s education            | 13.3 (1.9) year                 | 13.94 (2.2) year                |
| Father’s age                  | 33.2 (5.8) year                 | 32.4 (5.3) year                 |
| Father’s education            | 13.0 (2.4) year                 | 13.4 (2.2) year                 |
| Child’s gestational age       | 39.5 (1.5) week                 | 40.3 (1.1) week                 |
| Child’s birth weight          | 3344.6 (406) g                  | 3443.8 (313) g                  |
| No. of children in the family | 2.3 (1.3)                      | 2.4 (1.4)                      |
| Father DSM hyperactivity      | 15.7 (8.0)                      | 13.2 (7.0)                      |
| Father DSM inattention        | 12.9 (7.2)                      | 11.3 (6.9)                      |
| Father DSM total ADHD         | 25.5 (13.3)                     | 24.5 (11.9)                     |
| Mother DSM hyperactivity      | 14.1 (6.1)                      | 11.3 (5.1)                      |
| Mother DSM inattention ADHD   | 11.4 (6.5)                      | 8.8 (6.2)                       |
| Mother DSM total ADHD         | 25.5 (11.0)                     | 20.1 (9.2)                      |
| Note. SS = stop signal; ERP = event-related potential; BIDS = Ben-Gurion Infant Development Study; DSM = Diagnostic and Statistical Manual of Mental Disorders; ADHD = attention deficit hyperactivity disorder; CAARS = Conners Adult ADHD Rating Scale. |
The algorithm implemented the following rules: (a) If the participant succeeded in stopping, then it made the next stop trial more difficult by adding 50 ms to the delay; (b) If the participant failed to stop, then it made the next stop trial easier by subtracting 50 ms from the delay; and (c) If the participant responded before the stop signal was presented, then 50 ms was subtracted from the delay (this rule is critical for the tracking algorithm; otherwise, it gets trapped as the child continues to respond quickly to the go signal without being presented with the stop signals in any trial) and included the reaction time of this trial in the final analysis of the go trials. The tracking algorithm related to the set of the three games as a whole, meaning that the initial delay of the subsequent games was set to the delay value that the algorithm reached at the end of the previous game. The value of the delay was limited to the range between 0 and 1000 ms; reaction times shorter than 150 ms were discarded.

Dependent measures in this task were as follows:

1. SSRT (in milliseconds): the difference between mean RT of the go signal and the median delay.
2. Inhibition ratio: the percentage of trials in which the participant successfully stopped, among the total number of stop trials presented in the task.
3. Error proportion: the percentage of go trials in which the participant did not choose the correct response.
4. RT variability: the standard deviation of the choice reaction times of the participant in the go trials.

Figure 1. Panel A: Schematic representation of the stop-signal paradigm. Panel B: Three equivalent games measuring choice reaction times (go reaction time) based on color discrimination. From left to right: (a) sheep sorting to corresponding barns, stop signal: wolf; (b) apple sorting to corresponding baskets, stop signal: worm; and (c) flower sorting to corresponding vases, stop signal: mushroom.
Tracking-efficiency coefficient: the ability of the stop-signal program to track changes in the RT during the task. The coefficient was calculated based on the cross-correlation between ongoing changes in RT to go trials and the delays that the paradigm chose in the stop trials; it reflected the ability of the tracking algorithm to adjust itself to fluctuations in the child’s RT. The purpose of this measure was to verify the extent to which our tracking stop-signal paradigm was successful, even for children with high ratings of ADHD symptoms.

CAARS (Conners et al., 1998). The CAARS assesses ADHD and associated behavior in adults. In this study, we used the Diagnostic and Statistical Manual of Mental Disorders (DSM)–Hyperactive, and the total DSM–Manual of Mental Disorders assesses ADHD and associated behavior in adults. The correlations between the father’s self-report and the father’s report were both .79 for the Inattention scale, .78 and .80 for the Hyperactivity–Impulsivity scale, and both .86 for the total ADHD scale.

Procedures

The stop-signal testing was conducted individually in a quiet room, employing an HP IBM compatible laptop computer with a Windows 98 operating system and a screen size of 15 in. The left and right index fingers of the child rested on the response keys, which were keys A and L on the keyboard. The response keys were marked with two small stickers. Each child completed three games. The order of the games was counterbalanced between participants. Each game began with a practice block of the go discrimination task. The initial delay period was set as the mean RT of the first game practice block minus 300 ms (Logan, 1994). Then, the stop signal and stopping rule were explained to the child and an additional short practice block of mixed go and stop trials was carried out. Lastly, the 60 trials of the game were presented and the tracking paradigm was employed.

The study conformed to APA ethical standards receiving ethical approval from the Human Subject Research Committee of the Department of Psychology, Ben-Gurion University. Parents signed informed consent for the participation of their child in the research.

Analyses

Statistical analyses of behavioral data. Results were analyzed using the SPSS-9.0 (SPSS Inc., Chicago, IL) and STATISTICA-Windows version 8.0 (Statsoft, Tulsa, OK) software packages. First, we checked the data integrity and the efficiency of the tracking paradigm. Then, first-order correlations were calculated. Finally, multiple regressions were performed predicting SSRT and error rates. Significance levels were set to .05 in all analyses.

EEG and ERP recording and analysis. Electroencephalogram was recorded from 128 scalp sites using the EGI Geodesic Sensor net and system (Tucker, 1993). Electrode impedances were kept
below 40 KΩ, an acceptable level for this system (Ferree, Luu, Russell, & Tucker, 2001). All channels were referenced to the Cz channel and data collected using a 0.1–100 Hz bandpass filter, at 250 samples per second and digitized with a 16-bit AD converter.

Continuous EEG data were filtered with a 40 Hz low pass and segmented into 550 ms trials time locked to the presentation of the stop signal, with a baseline of 150 ms. At segmentation, trials were split into successful versus unsuccessful inhibition categories. The segmented data were inspected for artifacts. Segments with voltage deviations of more than 70 µV within eye channels were excluded for having eye movement or blinks. Channels with voltage deviations of more than 100 µV relative to baseline were marked as bad, and segments having more than 10 bad channels were excluded. Segments with <10 bad channels were included, and the bad channel data were replaced with spherical interpolation of the neighboring channel values. After cleanup, the mean number of good trials per condition for each participant was 20.4 (range = 10–32). After averaging, subsets were rereferenced using a polar average reference effect (PARE)-corrected average reference (PARE). The PARE-corrected average compensates for the bias by performing a spherical spline interpolation to estimate the voltages of the surface that is not covered by electrodes and baseline corrected.

The N2 was defined as the negative deflection peaking around 200 ms after the stop-signal presentation (specific time window: 118–242 ms), based both on preliminary inspection of the grand-average wave (see gray marked time window in Figure 2) and accepted timing for this component in the literature. N2 amplitude was calculated for each electrode as the adaptive mean within six samples around the minimum of the defined time window. Pearson correlations were calculated between the amplitude of the N2 for each electrode and the child’s concurrent ratings of ADHD symptoms. This procedure was applied for all of the electrodes. To reduce the possibility of Type I errors arising from multiple testing, we applied the False Discovery Rate control (FDR; Benjamini & Yekutieli, 2001), which has been validated and used in the literature when simultaneous comparisons are made, such as SPM analyses within the fMRI literature (Chumbley, Worsley, Flandin, & Friston, 2010).

P3 was defined as the positive peak within the time window following N2 (243–400 ms after stimulus presentation). The subsequent analysis procedure for the P3 was exactly the same that was used for the N2.

For the source localization analysis, we used standardized low-resolution brain electromagnetic tomography (sLORETA; Pascual-Marqués, 2002) to compute images of electric neuronal activity, which are used to estimate the electric neuronal generators involved in motor inhibition. On the basis of the scalp recorded electrical potentials, current density

![Figure 2](image-url)
estimates were extracted on a space of 6,239 voxels (voxel size: 5 × 5 × 5 mm), which was restricted to cortical gray matter and some hippocampi and amygdala, as defined by the digitized MNI152 template. Afterward, simple regression analysis was employed to determine whether the children’s hyperactivity scores were related to the observed electric neuronal activity associated with successful inhibition in the time window of 118–242 ms after the stop signal was delivered. The sLORETA output image represents the correlation coefficient of the regression analysis. The p values within sLORETA were calculated with a bootstrap method based on 5,000 iterations. Correlation coefficients higher than 0.67 were significant in a two-tailed test based on statistical nonparametric mapping, which was used to correct for multiple testing.

Results

Behavioral Results

Checks on data integrity and efficiency of the paradigm. The inhibition ratio of the sample was 59.1% (STD 8.9). This result was the first indication that the tracking paradigm successfully worked with this age group. It was consistent with previous findings, which show that for children the tracking paradigm produces inhibition ratios around 60% (see equivalent data reduction and inhibition ratios in Tillman et al., 2008).

To further verify the extent to which our tracking stop-signal paradigm was successful, even for children with high ratings of ADHD symptoms, we calculated a tracking-efficiency coefficient for each individual child that reflected the ability of the stop-signal program to track changes in the RT during the task (see more details in Figure 2). We found no significant correlations between the tracking-efficiency coefficient and concurrent ADHD symptoms of the child (r = .11, p = .52; r = −.05, p = .76; and r = .22, p = .20 for hyperactivity, inattention, and total ADHD symptoms, respectively). We found no significant correlations between the tracking-efficiency coefficient and paternal total ADHD and hyperactivity symptoms (r = .09, p = .49; r = −.06, p = .68, respectively). However, there was a borderline correlation with paternal inattentiveness (r = .23, p = .09). Therefore, the tracking-efficiency coefficient was controlled for in the multiple regression analysis predicting SSRT. Reaction time variability correlated with error rates (r = .49, p < .001). Therefore, although RT variability was not correlated in our study with paternal risk, this variable was controlled for in the multiple regression analyses predicting error rates.

As seen in Table 3, the inhibition ratio was not correlated with risk, but it was negatively correlated with SSRT (r = −.53, p < .001), meaning that regardless of their degree of risk, children with longer SSRTs were those with lower rates of successful inhibition. The inhibition ratio did not correlate with error rates (r = .08, n.s.). Given the relation between SSRT and the inhibition ratio, the multiple regression analysis described below was conducted by controlling for this variable to test whether the effect of paternal risk on SSRT would be obtained beyond the inhibition ratio contribution.

Correlations Between Longitudinal Measures and Performance in the Stop-Signal Task

Table 2 presents the descriptive statistics of the measures in our sample, and Table 3 presents the zero-order correlations among these measures. As can be seen, SSRT was correlated with paternal inattentiveness (r = .27, p < .05), whereas error rates were correlated with paternal total ADHD and hyperactivity symptoms (r = .30, p < .05 and r = .29, p < .05, respectively). SSRT was also correlated with concurrent ratings of the child’s hyperactivity (r = .41, p < .01). No significant correlations were found with mothers’ symptoms.

Multiple Regression Analysis

Predicting SSRT. Hierarchical multiple regression was conducted to predict SSRT, first entering the
variables that we wanted to control for and then entering the father inattentiveness predictor. This order was chosen to test whether the paternal symptoms measured 5 years before the performance of the stop-signal task made a significant contribution to SSRT variance beyond the contribution of the controlled variables (inhibition ratio, tracking efficiency; the variable of error rates was also initially entered into the multiple regression analysis for predicting SSRT as a controlled variable. However, since it was not found to contribute significantly \( p > .5 \), it was excluded from the final model).

The results showed that father inattentiveness had a significant contribution beyond the controlled variables: The \( F \) change between the models with and without this variable was \( F_{\text{change}}(1, 52) = 4.8, p = .033 \), contributing an additional 5.4\% to the explanation of the SSRT variance. As seen in Table 4, all three variables had significant separate effects and altogether explained 41\% of the SSRT variance, \( R^2 = .41 \), \( F(3, 52) = 12.11, p = .00 \), despite the fact that they were intercorrelated with some extent.

**Predicting error rates.** The same approach was taken for analyzing error rates. Here, the variable SSRT was entered as a controlled variable, but then was excluded as it did not contribute any significant independent explanation to the variance. Results indicated that the father hyperactivity predictor had a significant contribution: The change between the models with and without this variable was \( F_{\text{change}}(1, 53) = 4.04, p = .05 \), contributing 5.4\% to the explanation of the error rate variance. As seen in Table 5, the overall model explained 29.5\% of this variable’s variance, \( R^2 = .30, F(2, 53) = 11.08, p = .00 \).

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**Table 3**

*First-Order Correlations Between All Variables*

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<td>.31</td>
<td>.41</td>
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<td>10. RTsd</td>
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<td>-.15</td>
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<td>-.12</td>
<td>-.08</td>
<td>.49</td>
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**Note.** Bold = \( p < .05 \); bold & underlined = \( p < .01 \); italics = marginal effect. SS = stop signal; ADHD = attention deficit hyperactivity disorder; RT = reaction time; Hyper = hyperactivity; Inatt = inattentiveness; mGRT = mean Go RT; % err = error rates; RTsd = RT variability; Inhib R = inhibition ratio.
ERP Results

As seen in Figure 3A, children with high ratings for ADHD symptoms, especially hyperactivity, had reduced N2 amplitudes (less negative voltages). The correlation analysis indicated that 41 electrodes had significant correlations with these concurrent symptoms. These electrodes showed positive correlations, ranging between $r = .47$ and $r = .74$, that is, reduced N2 for children with higher symptoms.

Figure 3. (A) Event-related potential wave plot at Cz for children having high and low ratings for hyperactivity symptoms (groups defined by median split) in trials of successful inhibition. Gray area delineates the N2 time window. (B) Topographic map of voltages on the scalp at the N2 time window (specifically at 193 ms after stop-signal presentation). From left to right: Children with low hyperactivity rates, high hyperactivity rates, and the diff-wave between those two groups. Red circle defines the scalp area where all the significantly correlated electrodes were located. Red-blue arrows indicate a hypothetical source dipole consistent with both the scalp topographic localization of the effect and the source localization found in the standardized low-resolution brain electromagnetic tomography (sLORETA) analysis. (C) sLORETA results presented in horizontal, sagittal, and coronal cuts of the standardized Talairach brain template. Color palette indicates correlations of activity level with the child hyperactivity symptoms at the age of 4.5 years.
Interestingly, as displayed in Figure 3B at the right-most plate, these electrodes were topographically concentrated in a clear right parieto-occipital scalp area (the red circle defines the scalp area where all the significantly correlated electrodes were located). The majority of these correlations were still significant, even after controlling for multiple comparisons by applying the FDR procedure (25 of the 41 electrodes were found to have significant correlation with symptoms without the FDR correction, plus 1 other electrode with borderline significance). The scalp distribution of the effect is consistent with the N2 ERP literature related to the stop-signal task (for a review, see Folstein & Petten, 2008). The results of the sLORETA source localization analysis provide another interesting explanation of such a distribution in the current study: The source localization analysis showed that although several brain areas, including right frontal areas, showed some degree of correlation with the child’s ability to inhibit, the most significant and extensive brain region showing correlation with the child’s symptoms in our study was found to be the left frontal region, mainly the left medial and superior frontal gyri, the left insula, and the left superior temporal gyrus (see Figure 3C). Children with higher ratings of hyperactivity had less activity in these areas. This localization makes sense when considering the topographic distribution of the difference effect on the scalp; it is consistent with the idea of a dipole localized at the tempororo-frontal left brain area, with its negative pole pointing up toward the right parieto-occipital areas and its positive pole pointing down toward the left cheek. Regarding the P3, although the expected effect was obtained with standard scalp distribution and timing, no correlations with child symptoms were significant.

Discussion

In this study, we tested 5-year-old boys participating in a longitudinal study of risk for ADHD using a staircase dynamic-tracking stop-signal paradigm that was designed especially for preschoolers. We found that SSRT was correlated with concurrent symptoms of hyperactivity in the child. This supports the extant literature using variations of the stop-signal task in nonclinical populations, which consistently finds relations between performance in this type of task and ADHD symptoms (Pliszka et al., 1997; Tillman et al., 2008; although in this study, the correlation with SSRT was found with the child’s inattention symptoms). According to the “horse-race model,” the stopping process is slower and less efficient in children with more symptoms of ADHD and, as a consequence, challenges their ability to inhibit a response. In this sense, our findings are consistent with Barkley’s (1990, 1997) conceptualizations that a core deficit in inhibitory control underlies the development of broader deficits in executive functions, such as those seen in ADHD. Our findings are also consistent with other studies that have found inhibition deficits in ADHD (see Nigg, 2001, for comprehensive reviews of this literature); although, as Nigg, Willcutt, Doyle, and Sonuga-Barke (2005) have suggested, a control inhibition deficit might not characterize all children with ADHD. Alternative explanations have been proposed to explain the self-regulation problems seen in children with ADHD. These alternative views maintain that such deficits reflect lower level problems in regulation of arousal or motivational state (Sergeant, Oosterlaan, & van der Meere, 1999; Sonuga-Barke, Dalen, & Remington, 2003). This study cannot differentiate between these explanations. The fact that SSRT was not correlated with concurrent symptoms of inattention in the child could indicate that parental reports of hyperactivity are more reliable than their reports of inattention. We reported a similar trend in a previous BIDS publication (Auerbach et al., 2010), and suggested that at this age, parents may be more sensitive to symptoms of hyperactivity and impulsivity than to attentional difficulties, which may only become prominent when the children are in a school setting.

The advantage of our longitudinal design was the ability to test the effects of paternal ADHD risk on child outcome assessed 5 years after the paternal assessment. We found that fathers’ inattentive symptoms made a significant contribution to the explanation of SSRT, even when the effects of plausibly interfering variables were controlled. These variables included the inhibition ratio of the specific child and the efficiency of our paradigm to track the performance of the specific child. Correlations usually do not provide us with the direction of the causal relation; however, in our case, this causal direction is supported by the timing of data collection, as the data on the father’s ADHD symptoms were collected almost 5 years before the child performed the stop-signal task. Readers should note that for each parent, symptoms were estimated based on the combined self and spouse reports, a procedure that may have enhanced the reliability of these estimations.
The predictive correlation between paternal ADHD symptoms and the performance of the child in the stop-signal task indicates that young children at familial risk for ADHD show less optimal inhibitory control; indeed, this deficit has been suggested to be an endophenotype of the disorder (Castellanos & Tannock, 2002). Interestingly, only the paternal symptoms correlated with the performance variables in the stop-signal task, whereas maternal symptoms did not correlate with the child’s performance at all. This result is consistent with the literature indicating that for boys, there is stronger heritability for paternal than maternal ADHD symptoms (Minde et al., 2003). Our previous findings suggest that this familial risk is partly related to genetic and early temperamental differences (Auerbach, Landau, Arbelle, Berger, & Karplus, 2005; Auerbach et al., 2004) and to parental responsivity to the child (Landau et al., 2009). A similar interpretation could also be relevant for the correlations found in this study between parental ratings of child hyperactivity or impulsivity and the performance of the child on the computerized task. It could be that parents who perceive their child as being less able to self-regulate, raise a child who has lower inhibitory capacities, resulting in a self-fulfilling prophecy. An alternative interpretation would be that parents know their child best; therefore, they can accurately report on their child’s inhibitory control difficulties, such as ADHD symptomatology, and these difficulties are validly reflected in the child’s performance on the computerized task. Based solely on the results of this study, we cannot know which of these interpretations is more likely. Moreover, both interpretations could be valid to some extent and contribute to the developing child’s phenotype.

It is also worth noting that although the level of hyperactivity symptoms of the child was related to SSRT, it was not the hyperactivity of the father, but his inattentiveness, which predicted it. Consistently, Castellanos and Tannock (2002) concluded in their review that the strongest predictor for response inhibition deficits is inattention. They further suggest that recent evidence, pointing to inattention as the strongest predictor of slowed response inhibition, raises the possibility that impaired stop-signal inhibition could be an endophenotype for the inattention symptom cluster rather than for ADHD per se (although, in our sample, we found no significant correlation between the child’s inattention at the age of 4.5 years and SSRT). In contrast, the error rates of the child were related to the father’s hyperactivity.

In other words, our results indicate a differential pattern of risk: Hyperactivity was found to be related to error rates, whereas the father’s inattentiveness was found to be related to SSRT. This seems to suggest a plausible dissociation between cognitive endophenotypes for the different symptomatic dimensions of ADHD.

We did not find evidence that RT variability per se was related to paternal risk or to concurrent ADHD symptomatology in the child. This was an unexpected result, as this association has been frequently found in other studies (Kuntsi & Klein, 2012). The efficiency of the tracking paradigm is certainly affected by fluctuations in child performance. Therefore, it might well be that our tracking-efficiency coefficient reflects and crystallizes the instability of the child’s performance. If this is the case, then this measure might conceptually capture what, in other studies, has been reflected in RT variability. For example, two children could have the same amount of variance within their responses, while having very different profiles of performance instability or varying degrees of chaos or predictability. While the RT variability in these children would be the same, their tracking-efficiency coefficient would differ. In this sense, the tracking-efficiency measure shows more sensitivity to individual differences; in fact, in our study, there was a borderline correlation between tracking-efficiency coefficient and paternal inattentiveness.

The second part of this study focused on the brain activity underlying the deficit in inhibition seen in our stop-signal tasks. For this purpose, a subset of the children performed the stop-signal task while their electrophysiological brain activity was measured with the EEG or ERP technology. A clear N2 was found, consistent with the stop-signal and Go-NoGo ERP literature (see a review in Berger, 2011). The scalp distribution of this component is also suggestive of its involvement in attentional and categorizational processes (Folstein & Petten, 2008). The main difference between children scoring high and low in ADHD (especially hyperactivity) symptoms was found over the right parieto-occipital scalp areas. Localization of this effect using sLORETA indicated that the source of it was in the left fronto-temporal region, including the insula. This brain area was less recruited by children having higher ratings of hyperactivity. This localization is reasonable for explaining the voltage topography on the scalp; however, this finding should be interpreted with caution, since it is based on adult brain templates. Still, the result is extremely interesting in light of the findings of Bunge and colleagues.
(Bunge et al., 2002), who found that for adults, successful inhibition is related to the activation of right prefrontal brain areas, whereas in normally developing children, successful inhibition is related to the activation of language areas such as the left insula and left inferior frontal gyrus. Young children seem to rely more on verbal strategies than adults do when performing a challenging task. This idea was raised many years ago by Vygotsky, who studied the notion of private speech as a critical technique for controlling actions and thoughts (Berk & Winsler, 1995; Vygotsky, 1934/1962), especially at the preschool age. Our results indicate that preschool children who receive high ratings of hyperactivity are less able to recruit the brain circuitry that is known to be critical for successful inhibition. At least at this young age, the deficit associated with ADHD might be based on difficulties in utilizing verbal strategies for self-regulation. This suggestion is consistent with the predictions of Barkley’s model (Barkley, 1997) and the reports in the literature indicating that children with ADHD show less mature private speech while confronting a challenging task (Berk & Potts, 1991; Winsler, 1998). In contrast, many studies of older children have consistently shown that failures of inhibition in ADHD are related to volumetric as well as functional differences at the right prefrontal cortex, the basal ganglia, and mainly at the head of the caudate (see review in Berger, 2011). The brain circuitry function related to ADHD symptoms in our preschool-age participants differs from the circuitry usually found in previous ERP studies comparing school-age children with ADHD to school-age children without ADHD (Liotti, Pliszka, Perez, Kohmann, & Woldorff, 2005; Pliszka et al., 2000). The difference in results is most likely explained by the age of our participants, since there are known developmental differences in the mechanisms that preschool children versus older children recruit when required to inhibit. An alternate interpretation of our sLORETA findings is in terms of impaired response selection, as there are fMRI data relating the left inferior frontal gyrus to broad forms of controlled selection at the response and motoric level (Zhang, Feng, Fox, Gao, & Tan, 2004).

To summarize, we traced possible early pathways of a deficit in inhibitory control in children at familial risk for ADHD. Although, at this stage, we do not have formal diagnoses of the children, it is already evident that some of the children of fathers with ADHD symptoms, particularly inattention, show early difficulties with inhibition, a critical aspect of self-regulation. These difficulties are reported reliably and consistently by the parents and can be objectively measured in laboratory tasks of inhibitory control, such as the stop-signal task. The findings of this study strengthen the contention that behavioral markers of ADHD can be found very early in life. Moreover, we have shown a plausible brain basis of this behavioral difficulty in those preschool children showing high levels of hyperactivity symptoms.

The main strengths of the current study are its longitudinal nature and its multimeasure, multisource approach to data collection. The longitudinal nature of the study gave us the unique opportunity to assess the long-term effects of a risk factor, such as parental ADHD symptoms, on the very specific outcome of inhibitory control. Moreover, our study relied on a variety of measures that complemented and strengthened each other. First, we used questionnaires; for these type of data, we used the combined reports of both parents to enhance reliability. Second, our measures included a behavioral stop-signal task that was developed and specifically adapted for the preschool age, as this age is the critical period for the development of the relevant ability, in this case, inhibitory control. Lastly, we included electrophysiological brain activity information, which points to one of the plausible neuronal bases of failure.

Although the results are strong and statistically significant, an evident limitation of this study is the relatively small sample of participants and the even smaller sample of children that were subject to the entire set of measures. The lack of demographic differences between those who participated in this part of the study and the complete BIDS sample suggest that our findings are not unique to the subsample. An additional limitation of our study relates to the fact that parental ADHD risk is based on the reports of the parents themselves and not on clinical records or a psychiatric diagnosis of ADHD. However, as our results showed, the combined reports from the mother (about the father) and self-reports of the father had meaningful, predictive power. Lastly, our sample is limited to boys. As we mentioned in our previous publications (Auerbach et al., 2004; Auerbach et al., 2005), the decision to limit the sample to boys was made in light of the fact that the prevalence of ADHD is higher among boys than girls; therefore, by limiting the sample to boys, we increased the probability of having an adequate sample of children who would eventually develop ADHD. However, having a boys-only sample potentially, but not necessarily, limited the ability to generalize our findings.
References


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