Altered Performance on an Ocular Fixation Task in Attention-Deficit/Hyperactivity Disorder

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Background: *Attention-deficit/hyperactivity disorder (ADHD) is a common psychiatric disorder without validated objective markers. Eye movement studies may be useful in providing objective criteria for characterizing the disorder.*

Methods: *We compared 53 children (29 girls) with ADHD to 44 healthy control children (18 girls) on a 21-sec fixation task. Large saccades (> 4°) away from the fixation point were analyzed.*

Results: *Children with ADHD made more large saccades that interrupted fixation than did control children (*p = *.001). Mean scores of the ADHD group did not change significantly with subsequent retesting on placebo (*p = *.11); however, there was poor intrasubject correlation (*r = *.16).*

Conclusions: *Both boys and girls with ADHD made significantly more intrusive saccades during fixation than did control subjects, possibly reflecting intrinsic neurologic dysfunction; however, a probable "floor effect" obviates conclusions about the reliability of this measure.*
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Key Words: Fixation, attention, saccades, attention-deficit/hyperactivity disorder, eye movements

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common disorder, estimated to affect up to 11% of grade-school-age children (Gaub et al 1997; Wolraich et al 1996). Pathogenic models hypothesize frontal-striatal-cerebellar dysfunction (Castellanos et al, 2001). To date, however, there are no validated objective measures useful in determining the diagnosis (American Psychiatric Association 1994).

Eye tracking tasks are appealing as biological markers of disease because they are objective, painless, and noninvasive, and they can provide insight into the underlying neurophysiology. For example, children with ADHD have been shown to perform abnormally in eye movement tasks such as the go–no-go, delayed response, prosaccade, and antisaccade tasks that are presumed to involve prefrontal dysfunction (Castellanos et al 2000; Munoz et al 1999; Ross et al 1994, 2000a; Trommer et al 1988, 1991). By contrast, smooth pursuit eye movements are normal in children with ADHD (Castellanos et al 2000; Jacobsen et al 1996; Ross et al 2000b).

Frontal and striatal regions have also been implicated in a simpler task, visual fixation (Leigh et al 1999; Wurtz et al 1989). Before the availability of explicit diagnostic criteria for ADHD, hyperkinetic boys comorbid for a learning disability were shown to differ significantly from control subjects in the length of total fixation over a 20-sec time period (Shapira et al 1980). More recently, Munoz et al (1999) reported a significantly increased number of saccades in children with ADHD during a brief (less than 2-sec) portion of a complex task, the prosaccade task. We sought to confirm these findings of abnormal performance on a task requiring minimal instructions and to determine whether it may represent a stable trait marker.

Methods and Materials

Subjects

A sample that included 24 boys (mean age ± SD, 10.0 ± 2.0 years) and 29 girls (8.8 ± 1.6 years) with DSM-IV combined type ADHD between the ages of 7 and 13 was recruited from local schools. Twenty-six unrelated, age-matched boys (10.3 ± 1.5 years) and 18 girls (9.4 ± 1.7 years) aged 7 to 13 were recruited from the community as control subjects. Details of assessment and inclusion criteria were previously published, along with three other eye tracking tasks in the girl subjects (Castellanos et al 2000).

The local institutional review board approved the study, and written informed consent and assent were obtained from a parent and each subject, respectively.

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Eye Tracking Procedure

All subjects were administered a battery of eye movement tasks, including the one reported here, during a single session in a quiet and completely dark testing room. Angular position of the left eye was measured using the Ober2 infrared orbital scanning system, which uses infrared sources and sensors mounted inside goggles (Permobil Meditech, Woburn, MA). This system uses brief pulses of infrared light at a rate of 600 Hz and collects each data point over a few microseconds with a time constant under 1 msec.

In this specific task, subjects were instructed, "During this test the dot will stay in the center for about 30 sec, and then it will bounce back and forth across the screen. Follow it with your eyes." After an invariant 10-sec calibration interval, the fixation target (a white square .3° per side) was shown in the center of the screen for 21 sec. Head motion was minimized with a bite bar.

Eye position data were transferred to a computer where an automated procedure identified saccades (peak velocities greater than 25°/sec, an initial acceleration of greater than 1500°/sec^2, and a minimum duration of greater than 8 msec as saccades) and removed artifacts caused by eye blinks. Visual inspection was used to check for computer error and to be certain children were engaged in the task. We chose to count saccades larger than 4° as an index of failure to maintain attentional fixation during the 21-sec period. In addition, saccades between 1° and 4° were measured in a subset of 47 subjects (all girls) to confirm that large saccades are preferentially affected in ADHD as they are in frontal lobe dysfunction (Guitton et al 1985; Pierrot-Deseilligny et al 1991).

Control subjects were tested once. Patients were tested after a medication-free period of at least 10 days. To evaluate the temporal stability of this measure, we examined 23 girls who were tested during medication-free baseline and retested 3 to 9 weeks later while receiving double-blind placebo as a portion of a controlled trial (Sharp et al 1999).

Two-way ANOVA (diagnosis and gender) were performed on SPSS for Windows (Statistical Package for the Social Sciences, version 10). Test–retest data were analyzed by paired *t* test and Pearson correlation.

Results

Girls with ADHD did not differ significantly from female control subjects in the number of small saccades (1°–4°) during a simple prolonged fixation [ADHD mean (SD) 4.3 (5.1), control subjects 3.3 (4.3); $F(1, 45) = .54$, $p = .46$]; however, as shown in Figure 1, children with ADHD made significantly more large saccades than did matched control children [$F(1, 93) = 11.5$, $p = .001$]. Gender did not influence the number of erroneous large saccades [$F(1, 93) = 1.39$, $p = .24$] and there was no interaction between gender and diagnosis [$F(1, 93) = .025$, $p = .88$]. Within our restricted age range, there was no significant correlation between performance and age in any of the subgroups or in the group as a whole. Mean performance on this task

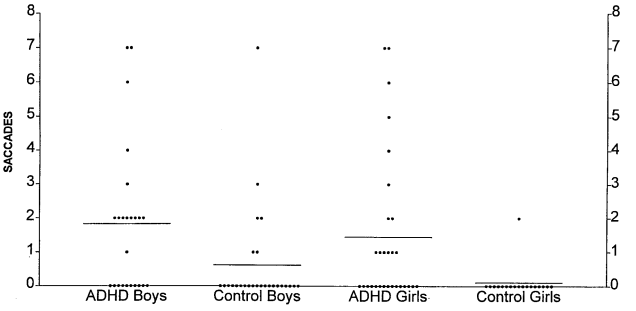

Figure 1. Number of saccades compared by group and gender. Horizontal bars denote mean values. Boys with attention-deficit/hyperactivity disorder (ADHD) produced a mean of 1.83 (± 2.20) saccades compared with .62 (± 1.53) for control boys. Girls with ADHD produced a mean of 1.45 (± 2.21) saccades compared with .11 (± .47) for control girls. Overall, children with ADHD (1.62 ± 3.16) made more saccades than did control children (.41 ± 1.23, $p = .001$).

was not significantly different between initial baseline session and subsequent retest while on placebo 3 to 9 weeks later (1.74 ± 2.7, .74 ± 1.5, $p = .11$); however, test–retest reliability was poor (Pearson $r = .16$). Thus, although mean errors were similar on retest for girls with ADHD, individual children varied considerably.

Discussion

Children with ADHD, whether boys or girls, made a significantly greater number of large saccades on a simple fixation task lasting 21-sec when compared with control children. Testing was in a quiet, completely darkened room, free of apparent distractions. Furthermore, the tendency to look away from a central fixation point did not improve significantly with retesting several weeks later; however, the test–retest correlation for 23 girls was poor ($r = .16$). This suggests that fixation errors in this task are a correlate of ADHD similar to subtle (soft) neurologic signs in that they provide good between-group separation but are not always reliable within a given individual (Denckla et al 1978, 1992); however, the presence of a substantial "floor effect" does not allow us reach firm conclusions regarding test–retest reliability for this measure. Further examination of this or similar tasks may potentially reveal a reproducible biological phenotype.

In contrast to prior fixation studies that involved a distracting stimulus, (Castellanos et al 2000; Munoz et al 1999; Ross et al 1994, 2000a; Trommer et al 1988, 1991), in our study, the only visual stimulus was the fixation target, which remained stationary in an otherwise completely dark room. Thus, the large saccades that interrupted fixation were not a failure to inhibit a maladaptive response to external stimuli, but rather a primary failure of visual fixation. These data provide evidence that children

with ADHD not only have difficulty inhibiting prepotent responses (Munoz et al 1999) but also have difficulty maintaining fixation in the absence of identifiable external or internal distracters, which is consistent with a failure of "top-down" regulation mediated by frontal-striatal dysfunction (Hikosaka et al 2000).

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