

# Altered Control of Visual Fixation and Saccadic Eye Movements in Attention-Deficit Hyperactivity Disorder

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**Munoz, Douglas P., Irene T. Armstrong, Karen A. Hampton, and Kimberly D. Moore.** Altered control of visual fixation and saccadic eye movements in attention-deficit hyperactivity disorder. *J Neurophysiol* 90: 503–514, 2003. First published April 2, 2003; 10.1152/jn.00192.2003. Attention-deficit hyperactivity disorder (ADHD) is characterized by the overt symptoms of impulsiveness, hyperactivity, and inattention. A frontostriatal pathophysiology has been hypothesized to produce these symptoms and lead to reduced ability to inhibit unnecessary or inappropriate behavioral responses. Oculomotor tasks can be designed to probe the ability of subjects to generate or inhibit reflexive and voluntary responses. Because regions of the frontal cortex and basal ganglia have been identified in the control of voluntary responses and saccadic suppression, we hypothesized that children and adults diagnosed with ADHD may have specific difficulties in oculomotor tasks requiring the suppression of reflexive or unwanted saccadic eye movements. To test this hypothesis, we measured eye movement performance in pro- and anti-saccade tasks of 114 ADHD and 180 control participants ranging in age from 6 to 59 yr. In the pro-saccade task, participants were instructed to look from a central fixation point toward an eccentric visual target. In the anti-saccade task, stimulus presentation was identical, but participants were instructed to suppress the saccade to the stimulus and instead look from the central fixation point to the side opposite the target. The state of fixation was manipulated by presenting the target either when the central fixation point was illuminated (overlap condition) or at some time after it disappeared (gap condition). In the pro-saccade task, ADHD participants had longer reaction times, greater intra-subject variance, and their saccades had reduced peak velocities and increased durations. In the anti-saccade task, ADHD participants had greater difficulty suppressing reflexive pro-saccades toward the eccentric target, increased reaction times for correct anti-saccades, and greater intra-subject variance. In a third task requiring prolonged fixation, ADHD participants generated more intrusive saccades during periods when they were required to maintain steady fixation. The results suggest that ADHD participants have reduced ability to suppress unwanted saccades and control their fixation behavior voluntarily, a finding that is consistent with a fronto-striatal pathophysiology. The findings are discussed in the context of recent neurophysiological data from nonhuman primates that have identified important control signals for saccade suppression that emanate from frontostriatal circuits.

## INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD), characterized by the symptoms of impulsiveness, hyperactivity, and inattention, is a prevalent neurobehavioral disorder estimated to affect ~5% of children and, for some, these core symptoms

are believed to persist into adulthood (Barkley 1997). As part of these core behavioral symptoms, response inhibition, may be an important component of the disability because ADHD subjects have difficulty suppressing inappropriate behavioral responses (Mostofsky et al. 2001; Shue et al. 1992).

At present, the etiology of ADHD remains poorly defined. Several observations support a hypothesis of a frontostriatal deficit (Castellanos 2001), possibly involving dysfunction in dopamine transmission, which may produce the symptoms of ADHD. First, ADHD individuals lack adequate inhibitory control and often act impulsively (Chelune et al. 1986; Grodzinsky and Diamond 1992), which is a classic sign of frontal lobe dysfunction (Fuster 1997). Second, regional blood flow and glucose metabolic studies have revealed frontal and/or striatal abnormalities in ADHD individuals (Lou et al. 1984, 1989; Zametkin et al. 1990). Third, anatomical neuroimaging studies have revealed altered architecture in the frontal lobes, caudate nucleus, and rostrum of the corpus callosum (Castellanos et al. 1996a, 2001; Giedd et al. 1994; Rubia et al. 1999). Fourth, dopamine, an important neurotransmitter in the striatum and frontal cortex, has been implicated in the disorder (Levy 1991) because methylphenidate, the main pharmacotherapy for ADHD, blocks dopamine reuptake. Fifth, there is evidence for abnormal levels of catecholamine metabolites in the cerebrospinal fluid of ADHD subjects (Castellanos et al. 1996b).

Saccades are rapid eye movements used to move the high acuity fovea of the retina to visual targets for detailed visual analysis. Characteristics of saccades can be measured precisely, and several behavioral tasks have been designed to test specific aspects of oculomotor control (see Leigh and Zee 1999 for review). In addition, the premotor circuitry controlling eye movements is now understood at a level that is sufficient to provide a basis for designing and interpreting more complex experiments to probe higher brain functions (Moschovakis et al. 1996; Munoz et al. 2000; Wurtz and Goldberg 1989). Saccades can be divided into two broad classes: reflexive, sensory-triggered movements and volitional movements. Initiation of visually triggered saccades involves occipital and parietal cortex and their inputs to the superior colliculus, which then projects to the premotor circuit in the brain stem and cerebellum. Planning of volitional saccades and suppression of reflexive saccades is under the control of frontal cortex and

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basal ganglia, which also project to the superior colliculus and brain stem premotor circuit (Hikosaka et al. 2000; Munoz et al. 2000 Schall 1997 for review).

We hypothesize that because of the overlap in the brain areas implicated in ADHD and in the control of volitional saccade behavior, ADHD individuals will have difficulty suppressing reflexive saccades and generating volitional saccades. To test this hypothesis, we recorded the eye movements of children and adults diagnosed with ADHD and controls recruited to perform a series of saccadic eye-movement tasks. The pro-saccade task (Fig. 1A) is used to test the ability of subjects to generate reflexive, visually triggered saccades. In this task, subjects are required to look from a central fixation point (FP) to an eccentric target stimulus as soon as it appears. We hypothesize that ADHD subjects will not be impaired in this task. The anti-saccade task (Fig. 1B) is used to test the ability of subjects to suppress reflexive saccades and instead generate voluntary saccades. In this task, subjects must suppress the reflexive saccade to the eccentric stimulus and instead generate a voluntary saccade to the mirror position where no stimulus appeared. Recent brain-imaging studies have identified specific activation in the frontal cortex that varies between pro- and anti-saccade tasks (Connolly et al. 2000, 2002; Doricchi et al. 1997; Muri et al. 1998; O'Driscoll et al. 1995; Sweeney et al. 1996). In addition, neurophysiological studies in non-human primates have identified various frontal regions that are active in the anti-saccade task (Everling and Munoz 2000; Funahashi et al. 1993; Schlag-Rey et al. 1997). Clinical studies have identified specific deficits in anti-saccade performance in var-

ious patient groups with a pathophysiology affecting the frontal cortex and/or basal ganglia (Everling and Fischer 1998; Guitton et al. 1985). Because of the documented difficulties with response inhibition that are evident in ADHD, we predict that ADHD participants will have difficulty suppressing reflexive pro-saccades in the anti-saccade task.

There are both exo- and endogenous components of fixation control (Paré and Munoz 1996; Reuter-Lorenz et al. 1995). The endogenous component of fixation is required to maintain steady fixation independent of whether there is a visual stimulus on the fovea, whereas the exogenous component is mediated by the presence of a visible stimulus on the fovea. The presence or absence of the exogenous component influences performance in pro- and anti-saccade tasks (Fischer and Weber 1997; Munoz et al. 1998a). Removing the central FP prior to the appearance of the eccentric stimulus (gap task; Fig. 1D) reduces saccadic reaction time (SRT) and increases the percentage of direction errors on anti-saccade trials. In contrast, SRT is increased and error rates reduced when the FP remains illuminated during the appearance of the saccade target (overlap task; Fig. 1C).

We reason that if ADHD individuals have a frontostriatal deficit, then they will have difficulty maintaining the endogenous component of visual fixation. Such a deficit will result in difficulty regulating the processes of saccade suppression and saccade initiation, leading to the generation of more reflexive saccades and more direction errors in the anti-saccade task. Further, these deficits should be present in both gap and overlap conditions. We show that ADHD participants have difficulty maintaining endogenous fixation and suppressing reflexive saccades in the anti-saccade task, and they also have longer and more variable reaction times. Preliminary reports of these data have appeared (Munoz et al. 1998b, 1999).

## METHODS

### Subjects

All experimental procedures were reviewed and approved by the Queen's University Human Research Ethics Board. Participants between the ages of 6 and 59 yr were recruited from the greater Kingston area via newspaper advertisements and physician referral. They were informed of the general nature of the study prior to consenting to participate and were reimbursed \$10 per recording session. Parents provided informed consent for minors. All participants reported no known visual disorders other than refractive errors, and they were permitted to wear their prescription lenses during the recording sessions.

This report describes the eye-movement behavior of 294 participants sorted into four groups: control or ADHD children (age 6–16 yr) or adults (age 18–59 yr). Each of the four groups contained between 38 and 105 subjects (see Table 1). A portion of the data collected from control subjects was presented in a previous paper describing developmental changes in the control of visual fixation and saccade generation among normal subjects between the ages of 5 and 79 yr (Munoz et al. 1998a).

All 114 ADHD participants included in this report were diagnosed in the community, initially by various health care professionals. Diagnosis was confirmed and co-morbidity assessed during an interview with a clinical psychologist using DSM-IV criteria, Conner Parent's Rating Scales (CPRS) for children and the Brown Attention-Deficit Disorder Scale (BADDSS) for adults. Inclusion criteria for the ADHD pool included meeting DSM-IV criteria and criteria established from the CPRS (subjects 6–16 yr) or BADDSS (subjects 18–59

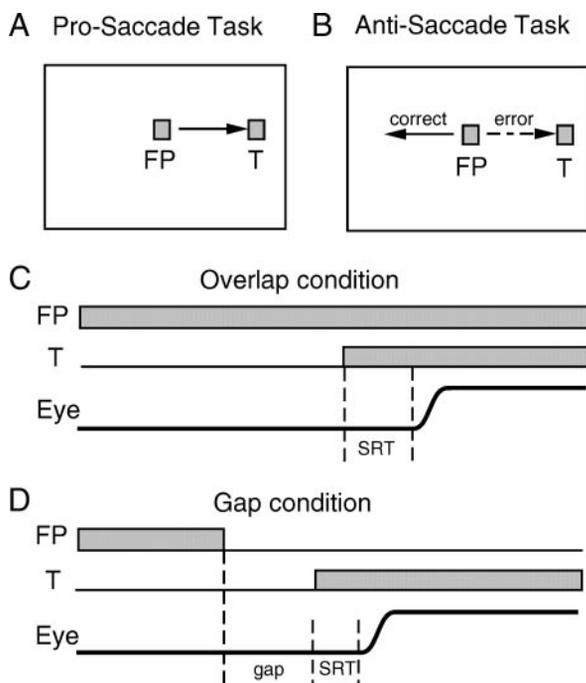


FIG. 1. Schematic showing the behavioral paradigms used. Within a block of trials, subjects were instructed to either look from the fixation point (FP) to the eccentric target (T) (A: pro-saccade task) or from the FP to the mirror position of the T (B: anti-saccade task). Solid arrows, the correct response; dashed arrow, a direction error. In the overlap condition (C), the central FP remained illuminated when T appeared. In the gap condition (D), the FP disappeared before T appearance. The gap duration was either kept constant at 200 ms or varied randomly from 0 to 800 ms (see METHODS). SRT: saccadic reaction time.

TABLE 1. Characteristics of subject pool utilized in the present study

Subject Group	n (Female)	Age	Handedness	CPRS	
				Hyperactivity	Impulsivity
Child					
Control	75 (35)	10.7 ± 0.3	7.8 ± 0.4	45.9 ± 1.0	47.2 ± 1.1
ADHD	76 (15)	10.3 ± 0.3	6.1 ± 0.6	84.1 ± 1.4	75.7 ± 1.3
Adults					
Control	105 (59)	34.2 ± 1.1	6.8 ± 0.4	—	—
ADHD	38 (20)	31.0 ± 1.4	4.8 ± 1.0	—	—

Values are means ± SE. Number of women in each group shown in parentheses. ADHD, attention-deficit hyperactivity disorder.

yr). Other ADHD participants ( $n = 34$ ; 23 children, 11 adults) were excluded because we identified the following co-morbid signs: learning disabilities resulting in delayed advancement in school, Tourette's syndrome, or bipolar disease. Control participants or their guardians reported no known neurological or psychiatric disorders. Control children were also assessed using the CPRS. Impulsiveness scores were reliably different between ADHD and control children (mean ± SD: ADHD:  $75.8 \pm 10.8$ ; control:  $47.1 \pm 9.1$ ),  $F(1,142) = 258.8$ ,  $P < 0.0001$ . Hyperactivity scores were also significantly elevated for the ADHD children (ADHD:  $84.2 \pm 11.5$ ; control:  $45.8 \pm 8.8$ ),  $F(1,142) = 443.97$ ,  $P < 0.0001$ . Only ADHD adults were administered the BADDSS, and all ADHD adults scored  $>50$  (range 64–96), which is indicative of ADHD.

Seventy-six of the ADHD participants (64/76 children, 12/38 adults) were on a prescribed drug treatment regime consisting of daily stimulant medication (e.g., methylphenidate, clyert) to help ameliorate the symptoms of the disorder. Data were collected from these participants on days when they did not take any prescribed drug treatment. The minimal time between the previous dose and testing for all participants was  $\geq 20$  h to minimize any carryover effects.

Handedness of all subjects was assessed with a modified version of the Edinburgh Handedness Inventory (Oldfield 1971). Participants were asked to rate hand preference in the following tasks: writing, drawing, throwing, using scissors, using a toothbrush, using a knife without a fork, using a spoon, swinging a hockey stick, turning a key, and opening a box. Each right-handed response was assigned +1 and each left-handed response was assigned -1. Therefore a score of +10 or -10 indicated extreme right- or left-handedness, respectively. Mean handedness scores are presented in Table 1. Most interestingly, control groups were significantly more right-handed than the ADHD groups,  $F(1,290) = 9.82$ ,  $P < 0.01$ . This trend toward non-right-handedness among the ADHD participants is consistent with previous reports (Reid and Norvilitis 2000) and may indicate anomalous laterality of function in ADHD.

### Experimental set-up and behavioral paradigms

Participants were seated upright in a dental chair equipped with a head rest that was adjusted for height so that they faced the center of a translucent visual screen, 100 cm away. The experiments were performed in darkness and silence except for the controlled presentation of visual stimuli that consisted of red light-emitting diodes (LEDs; chromaticity coordinates  $CIE_x = 0.73$ ,  $CIE_y = 0.26$ ). One LED ( $2.0 \text{ cd/m}^2$ ) was back-projected onto the center of the translucent screen and served as a central FP to start all trials. Eccentric target LEDs ( $5.0 \text{ cd/m}^2$ ) were mounted into small boxes positioned  $20^\circ$  to the left and right of the central FP. Between trials the screen was illuminated diffusely ( $1.0 \text{ cd/m}^2$ ) with background slides depicting various visual scenes to reduce dark adaptation and boredom.

In the pro-saccade task (Fig. 1A), participants were instructed to fixate initially on a central FP and then look from the location of the

FP to an eccentric target stimulus that appeared randomly either  $20^\circ$  to the left or right. Each trial began when the background illumination was turned off. After a 250-ms period of darkness, the FP appeared. After an additional 1,000 ms one of two events occurred. In the overlap condition (Fig. 1C), the FP remained illuminated when the eccentric target stimulus appeared. In the gap condition (Fig. 1D), the FP disappeared and, after a gap period of 200 ms, the eccentric target stimulus appeared. The target stimulus remained illuminated for 1,000 ms, after which all LEDs were turned off and the background illumination came on to indicate the end of the trial. Target location ( $20^\circ$  right or left) and fixation condition (gap or overlap) were randomly interleaved within a block of trials.

In the anti-saccade task (Fig. 1B), the presentation of stimuli was identical to that described in the preceding text. Participants were instructed to look at the central FP, but then, after the appearance of the eccentric stimulus, they were asked to look away from the stimulus, to the opposite side of the vertical meridian. Once again, stimulus location ( $20^\circ$  right or left) and fixation condition (gap or overlap) were randomly interleaved within a block of trials.

In a third experiment, designed to study the ability to maintain prolonged fixation, participants performed pro-saccades in the gap condition only. In this experiment, the FP was illuminated for 1,500 ms, and the gap period was varied randomly among one of five intervals: 0, 200, 400, 600, or 800 ms. The target then appeared randomly either  $20^\circ$  right (40% of trials) or  $20^\circ$  left (40% of trials), or the FP reappeared in the center of the screen (20% of trials).

The results of three separate experiments are described. In the first experiment, participants performed the pro-saccade task in randomized overlap and gap conditions with the gap duration fixed at 200 ms and the eccentric target stimulus appeared randomly  $20^\circ$  to the right or left of center. In the second experiment, performed on the same day, stimulus conditions remained identical but participants were instructed to generate anti-saccades after the appearance of the eccentric target stimulus. In the third experiment, performed on a separate day, participants were instructed to generate pro-saccades in the prolonged fixation experiment and the gap duration was varied randomly from 0 to 800 ms in 200-ms increments.

Experiments were conducted in two separate sessions separated by 1–14 days. In the first experimental session, participants completed one block of pro-saccades followed by two blocks of anti-saccades. Each block consisted of 80–120 trials equally distributed between gap/overlap and target right/left conditions. Participants were given no practice but were asked to repeat the task instructions prior to the onset of data collection. In the second session, participants returned to perform the prolonged fixation experiment with randomized gap durations, completing three blocks of 100–150 trials per block. All participants in the study completed the pro- and anti-saccade tasks on day 1. Only a subset of the participants (73%; 215 / 294) completed the prolonged fixation experiment on day 2. Each recording session lasted not more than 45 min, and there were breaks between blocks of trials during which participants were provided with snacks and drinks to maintain alertness.

### Data collection and analysis

Horizontal eye movements were measured using DC electrooculography (EOG). Ag-AgCl skin electrodes were placed bitemporally to record horizontal eye position. A ground electrode was placed just above the eyebrows in the center of the forehead. Participants were instructed to rest their head comfortably against the headrest and during data collection to move only their eyes. The EOG signal was amplified and low-pass filtered with a Grass P18 amplifier rated for human use. To minimize EOG drift, participants wore the electrodes for  $\sim 10$  min before the onset of calibration and recording. Calibration was performed by having participants look back and forth between the targets located at  $20^\circ$  right,  $20^\circ$  left, and the central FP. Calibration was repeated between each block of trials.

The experimental paradigms, visual displays, and storage of eye-movement data were under the control of a 486 computer running a real-time data-acquisition system (REX) (Hays et al. 1982). Horizontal eye position was digitized at a rate of 500 Hz. Digitized data were stored on a hard disk, and subsequent off-line analysis was performed on a Sun Sparcstation. Horizontal eye velocity was computed from the position traces by applying software differentiation (finite impulse-response filter). The onset and termination of each saccade was determined when eye velocity respectively increased or decreased beyond 30°/s. Saccades were scored as correct if the first movement after appearance of the eccentric stimulus was >5° in amplitude and in the correct direction (i.e., toward the stimulus in the pro-saccade task; away from the stimulus in the anti-saccade task). Saccades were scored as incorrect if the first saccade after appearance of the eccentric stimulus was in the wrong direction (i.e., away from the target in the pro-saccade task; toward the target in the anti-saccade task). SRT was measured as the time from stimulus appearance to the onset of the first saccade. Mean SRT in the pro- and anti-saccade tasks was computed from trials with reaction latencies between 90 and 1,000 ms. Movements were classified as anticipatory and were excluded from analysis if they were initiated <90 ms after target appearance. This anticipatory cutoff was obtained from viewing SRT distributions for correct and incorrect movements in the pro-saccade task (Kalesnykas and Hallett 1987; Munoz et al. 1998a). Saccades that were initiated <90 ms after target appearance were correct ~50% of the time, whereas saccades initiated >90 ms after target appearance were correct >95% of the time (see Fig. 2). We also computed the percentage of express saccades generated by each subject in all conditions. Express saccades are the shortest latency visually triggered saccades (Fischer and Rampsberger 1984; Fischer et al. 1993; Paré and Munoz 1996). In humans, they are initiated between 90 and 140 ms after target appearance. From the data of each participant, we computed the following values: the mean SRT for correct trials; the coefficient of variation of SRT for correct trials [ $CV = (SD / \text{mean}) * 100$ ]; the percentage of express saccades (latency: 90–140 ms); and the percentage of direc-

tion errors (saccades away from the target in the pro-saccade task; saccades toward the target in the anti-saccade task).

We also measured the amplitude, peak velocity, and duration of horizontal saccades made in the pro-saccade task only. This analysis was performed for data from 291 participants. Data from three participants (1 ADHD child, 1 control child, 1 control adult) were excluded due to abnormally high levels of noise in the EOG signals that compromised these measures. For all correct movements in the pro-saccade task initiated between 90 and 1,000 ms after stimulus appearance, we computed the mean amplitude of the first saccade following target appearance. Additionally, for saccades with amplitudes between 18 and 21°, we computed the mean peak velocity and duration. This narrow window of amplitudes was used to control for well-known main sequence effects of amplitude on velocity and duration (Leigh and Zee 1999). Subjects were not provided any feedback regarding the accuracy of their anti-saccades so that variability in the amplitude of these movements was considerable for participants of all ages. Thus anti-saccade amplitude, peak velocity, and duration were not quantified.

Intrusive saccades were identified as unnecessary rapid shifts in eye position that exceeded 2° in amplitude and 70°/s in velocity. We counted the number of intrusive saccades that occurred in the prolonged fixation experiment with randomized gap duration in two separate epochs: during the final 10,00 ms of visual fixation and during the randomized gap period.

The first two experiments (pro- and anti-saccade tasks) contained two within-subject factors: direction (right vs. left) and fixation state (gap vs. overlap); and two between-group factors: age (child vs. adult) and psychopathology (ADHD vs. none). Despite the fact that all subjects performed the pro-saccade task before the anti-saccade task, there were no differences in ordering affects between subjects groups. Perhaps even more surprising, the error rates from the first 20 anti-saccade trials did not differ significantly from the overall error rates among any of the groups. The third experiment (prolonged fixation with randomized gap) contained two within-subject factors: direction (right vs. left) and gap duration (0, 200, 400, 600, and 800); and two between-group factors of age (child vs. adult), and psychopathology (ADHD vs. none). All dependent measures were analyzed using ANOVA with alpha set at 0.05.

Because the focus of this paper is on differences between ADHD and control subjects, most analyses contrasted psychopathology with the within-subject factors separately for adults and children. Unequal sample sizes complicated analyses, especially for adults where the samples were extremely different (38 ADHD adults vs. 105 control adults). These extreme differences bring into question any interactions that we found among the data. We therefore randomly selected subjects to balance the number of subjects in the ADHD/control groups by age. In the case of the children's data, we removed three ADHD subjects at random from the analysis of each dependent measure. In the case of the adult data, we removed all but 38 of the control adults and performed an analysis on each dependent measure for groups of equal size. Because this excluded almost two-thirds of the adult control data, we performed the removal/analysis procedure several times. Because no differences were noted, we retained the unequal numbers of subjects because the control adult data are necessary to establish reliably the developmental trends presented in RESULTS.

## RESULTS

### Pro-saccade task

SRTs. Figure 2 illustrates the distribution of SRTs obtained from control and ADHD children and adults in the pro-saccade task with gap and overlap conditions. The vast majority of the responses were correct (positive values on the ordinate); only a very small percentage of responses were direction errors (negative values on the ordinate). For all subject groups, most

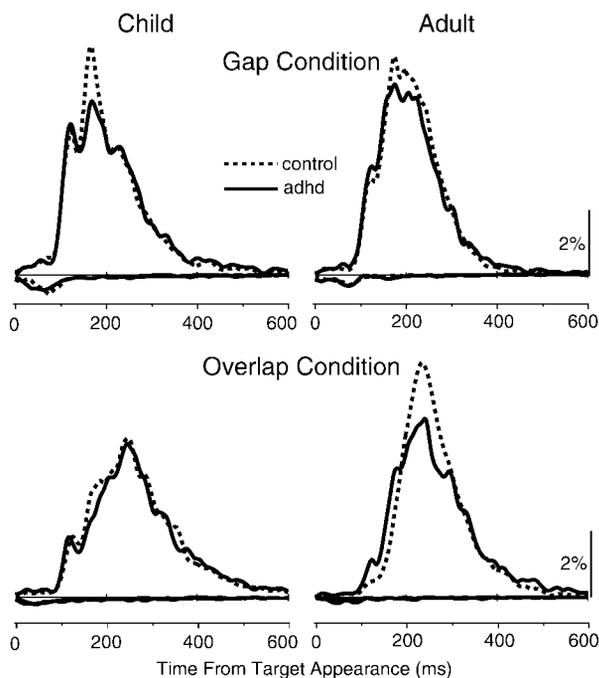


FIG. 2. Distribution of SRTs from all subjects in the pro-saccade task for gap and overlap conditions. Curves were generated by binning all latencies into 10-ms bins and then fitting a cubic spline function (de Boor 1978) through the data. —, attention-deficit hyperactivity disorder (ADHD); ···, control. Positive percentage on ordinate represents correct responses, whereas negative values represent direction errors.

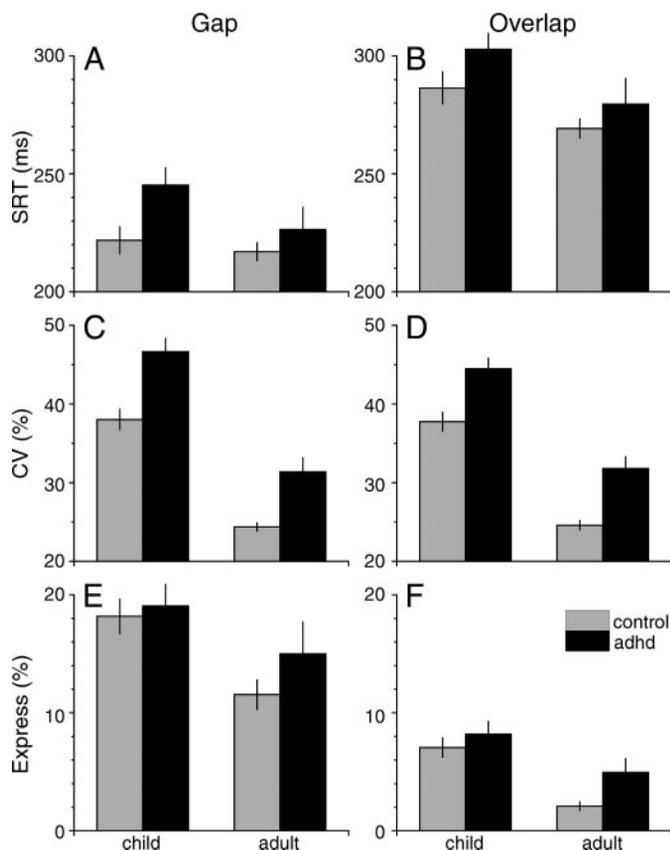


FIG. 3. Quantification of parameters in the gap (left) and overlap (right) conditions for the pro-saccade task. *A* and *B*: mean SRTs for correct responses. *C* and *D*: coefficient of variation (SD of SRT/mean SRT  $\times$  100%). *E* and *F*: percentage of express saccades (SRT: 90–140 ms). Values represent means  $\pm$  SE. Gap duration was fixed at 200 ms.

of the direction errors were triggered with reaction times  $<90$  ms and, presumably, were due to anticipation of target appearance because the distribution of correct and incorrect responses was mirrored during this interval. Among the correct pro-saccades initiated  $>90$  ms after target appearance, most were triggered before 300 ms in the gap condition and before 400 ms in the overlap condition.

From the correct responses initiated 90–1,000 ms after target appearance, we computed the mean SRT, the coefficient of variation in SRT, and percentage of express saccades for each participant in the gap and overlap conditions and then calculated mean values for each of the four groups (Fig. 3). Figure 3, *A* and *B*, illustrates the mean SRT in the gap and overlap conditions for the four subject groups. Mean SRT was significantly elevated in ADHD,  $F(1,290) = 5.06$ ,  $P < 0.05$ . Consistent with previous studies (Fischer et al. 1997; Kalesnykas and Hallett 1987; Munoz et al. 1998a; Saslow 1967), mean SRT for all groups was significantly increased in the overlap condition compared with the gap condition,  $F(1,290) = 719.01$ ,  $P < 0.001$ . This pro-saccade gap effect (overlap SRT – gap SRT), ranged from 52 to 64 ms and was larger for children than for adults,  $F(1,290) = 4.05$ ,  $P < 0.05$ . Consistent with a previous study (Cairney et al. 2001), there was no difference in gap effect between ADHD and control groups. We have reported previously the influence of age on SRT among control participants (Munoz et al. 1998a). The mean SRT for the children was greater than for the adults in both

control and ADHD groups,  $F(1,290) = 5.75$ ,  $P = 0.01$ . For all groups, there was a modest directional asymmetry with rightward pro-saccades having shorter mean SRT than leftward pro-saccades (Table 2). This directional asymmetry was specific to the overlap condition,  $F(1,290) = 28.66$ ,  $P < 0.001$  and more pronounced in the children  $F(1,290) = 3.59$ ,  $P = 0.05$ .

An analysis of intra-subject variance in SRT, expressed as the coefficient of variation (CV), revealed that ADHD participants were far more variable in the time of their responses,  $F(1,290) = 38.41$ ,  $P < 0.001$  (Fig. 3, *C* and *D*). In addition, responses of children were more variable than adults,  $F(1,290) = 135.36$ ,  $P < 0.001$ , as described previously (Munoz et al. 1998a). The differences between control and ADHD groups were consistent for children and adults; thus there was no interaction between the factors,  $F(1,290) < 1$ ,  $P > 0.80$ .

It has been suggested that abnormally high percentages of express saccades, especially in the overlap condition, may reflect underlying pathology in brain areas controlling visual fixation and/or saccade initiation (Biscaldi et al. 1996). We hypothesized initially that ADHD participants would make more express saccades than control participants. Figure 3, *E* and *F*, contrasts the percentage of express saccades for the groups in the gap and overlap conditions. All groups generated more express saccades in the gap, compared with overlap conditions,  $F(1,290) = 202.40$ ,  $P < 0.001$ . Consistent with previous reports (Fischer et al. 1997; Munoz et al. 1998a), children generated more express saccades than adults,  $F(1,290) = 14.65$ ,  $P < 0.001$ . Note, however, that although ADHD subject groups appeared to generate slightly more express saccades than control groups, this difference was not significant,  $F(1,290) = 2.82$ ,  $P > 0.05$ .

**METRICS.** ADHD and control children and ADHD adults showed no difference in the amplitude of the first saccade to target in the pro-saccade task, but control adults made larger saccades,  $F(1,287) = 4.76$ ,  $P < 0.05$  (control children,  $19.3^\circ$ ; ADHD children,  $19.3^\circ$ ; control adults,  $19.5^\circ$ ; ADHD adults,  $19.3^\circ$ ). For saccades between 18 and  $21^\circ$  in amplitude, there were significant differences in the duration and peak velocity of the saccades between the groups. First, compared with adults, children generated saccades with higher peak velocities [children:  $408^\circ/\text{s}$ ; adults:  $375^\circ/\text{s}$ ;  $F(1,287) = 18.07$ ,  $P < 0.001$ ], and shorter durations [children: 72.9 ms; adults: 78.7 ms;  $F(1,287) = 18.74$ ,  $P < 0.001$ ]. Second, control subjects generated saccades with shorter durations than ADHD subjects [ADHD: 79.0 ms; control 72.6 ms;  $F(1,287) = 23.69$ ,  $P < 0.001$ ], and peak velocity was larger for control compared with ADHD participants [ADHD:  $383^\circ/\text{s}$ ; control  $399^\circ/\text{s}$ ;  $F(1,287) = 4.48$ ,  $P < 0.05$ ].

TABLE 2. Mean saccadic reaction times of studied groups contrasting direction differences in correct responses

Subject Group	Pro-Saccade		Anti-Saccade	
	Left	Right	Left	Right
Child				
Control	257	253	367	356
ADHD	282	265	382	378
Adult				
Control	244	243	305	300
ADHD	255	252	335	321

## Anti-saccade task

SRTs. Figure 4 illustrates the distribution of correct and incorrect SRTs in the anti-saccade task. At latencies of  $<90$  ms, the distribution of correct and incorrect responses mirrored each other. However, in the interval 90–180 ms after target appearance, there were more incorrect responses than correct responses. Most interestingly, there was a paucity of correct responses in the interval spanning from 90 to 140 ms, the express saccade interval. Most correct responses were initiated only after 180 ms in both the gap and overlap conditions.

A comparison of the distribution of correct and error responses among ADHD and control participants revealed ADHD participants made more errors and the onset of correct responses of ADHD participants was more variable than the correct responses obtained from the control participants. This increase in the percentage of direction errors among the ADHD participants occurred across the entire range of error SRTs. An analysis of error SRTs was not possible due to the extreme variability in error rates among individual participants (see Fig. 6).

Figure 5, *A* and *B*, contrasts the mean SRT obtained in the anti-gap and anti-overlap conditions for the different subject groups. Note that the mean SRT of correct anti-saccades was significantly elevated for children compared with adults for both control and ADHD groups,  $F(1,290) = 46.42$ ,  $P < 0.001$ . More importantly, mean SRT was greater among the ADHD participants,  $F(1,290) = 7.24$ ,  $P < 0.01$ .

Mean SRT for correct anti-saccades was far greater than the

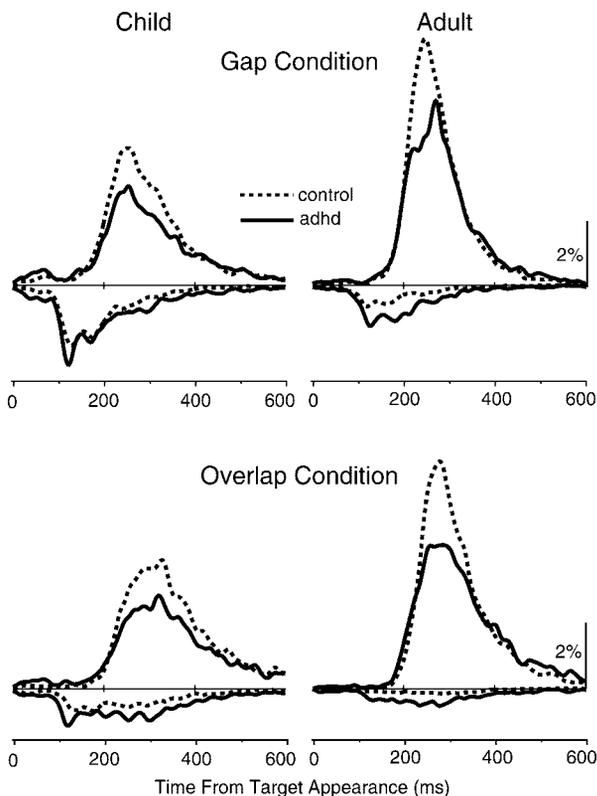


FIG. 4. Distribution of SRTs from all subjects in the anti-saccade task for gap and overlap conditions. Curves were generated by binning all latencies into 10-ms bins and then fitting a cubic spline function (de Boor 1978) through the data. —, ADHD; ····, control. Positive percentage on ordinate represents correct responses, whereas negative values represent direction errors.

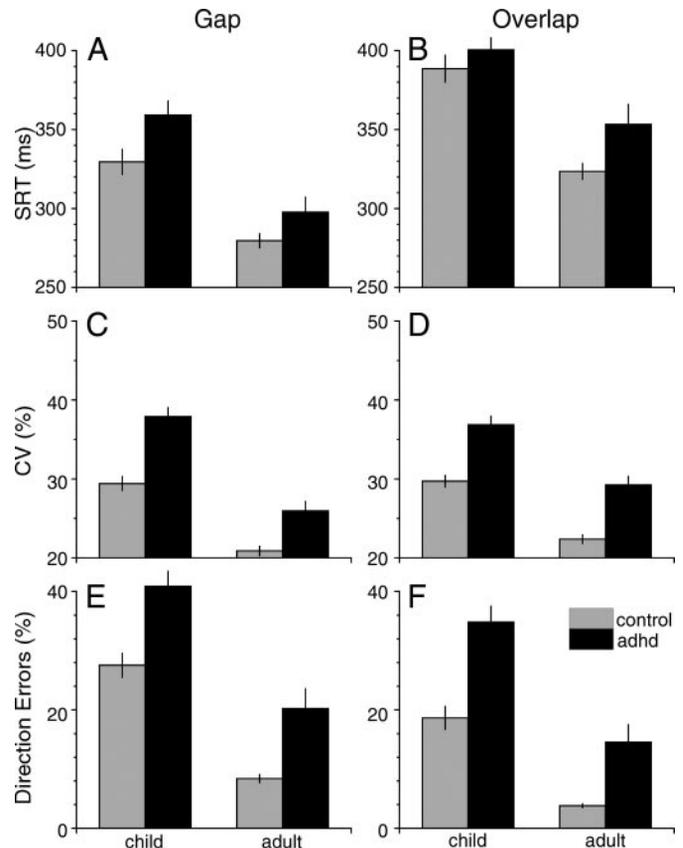


FIG. 5. Quantification of parameters in the gap (*left*) and overlap (*right*) conditions for the anti-saccade task. *A* and *B*: mean SRTs for correct responses. *C* and *D*: coefficient of variation (SD of SRT/mean SRT  $\times$  100%). *E* and *F*: percentage of direction errors in the anti-saccade task. Values represent means  $\pm$  SE. Gap duration was fixed at 200 ms.

mean SRT for correct pro-saccades,  $F(1,290) = 637.82$ ,  $P < 0.001$ . This anti-effect (anti-saccade SRT – pro-saccade SRT) was significant for each group, but the difference of SRT between tasks was larger in children than adults and increased from overlap to gap conditions for all groups except ADHD adults,  $F(1,290) = 5.28$ ,  $P < 0.05$ . Similar to pro-saccades, there was also a significant directional bias in anti-saccade SRT with all subject groups being faster moving to the right side,  $F(1,290) = 15.09$ ,  $P < 0.001$  (Table 2). There was also a significant gap effect (overlap SRT – gap SRT) among anti-saccades that ranged from 41 to 59 ms,  $F(1,290) = 584.96$ ,  $P < 0.001$ . The gap effect was larger for ADHD adults than for control adults and larger for control children than for ADHD children, resulting in an interaction of the factors of age and fixation state,  $F(1,290) = 12.06$ ,  $P < 0.05$ .

Figure 5, *C* and *D*, illustrates the intra-subject variance in SRT for the subject groups in the anti-saccade task. Once again, the amount of intra-subject variance in anti-saccade SRT, expressed as the CV, was elevated in the ADHD groups compared with the control groups,  $F(1,290) = 58.02$ ,  $P < 0.001$ . In addition, as with the pro-saccade task, the CV of children was significantly elevated compared with the adult values among both control and ADHD subjects,  $F(1,290) = 95.27$ ,  $P < 0.001$ .

**DIRECTION ERRORS.** The percentage of direction errors in the anti-saccade task is illustrated in Fig. 5, *E* and *F*. All groups generated more direction errors in the gap condition than in the

overlap condition,  $F(1,290) = 168.94$ ,  $P < 0.001$ , and the effect was greater for children resulting in an interaction between age and fixation state,  $F(1,290) = 5.44$ ,  $P < 0.05$ . In addition, ADHD participants generated a greater percentage of direction errors than did control participants,  $F(1,290) = 38.78$ ,  $P < 0.001$ . Consistent with previous studies (Fischer et al. 1997; Munoz et al. 1998a), children made significantly more direction errors than adults,  $F(1,290) = 83.79$ ,  $P < 0.001$ .

Figure 6 illustrates, in greater detail, the age-dependent changes in performance of the anti-saccade task for both ADHD and control groups. Performance, expressed as the percentage of direction errors, improved steadily across subject age from 6 to 16 yr. Among control participants, adult levels of performance were only achieved at approximately age 16 yr (see also Munoz et al. 1998a). As a group, the ADHD curve lagged the control curve and appeared to asymptote at a higher level. Most importantly, however, note that among both children and adult groups, some ADHD participants clustered along the control curve, whereas other ADHD participants were clearly impaired. Thus while some ADHD subjects had difficulties suppressing reflexive saccades, other ADHD subjects were no different from control subjects, suggesting that there may be subgroups within the ADHD spectrum.

#### Prolonged fixation task

The increased error rates in the anti-saccade task and the increased variance in SRT suggest that the ADHD groups had some difficulties in controlling or gating fixation signals. To evaluate fixation instability in greater detail, participants performed a separate experiment consisting of blocks of pro-saccade gap trials in which the FP was visible for 1,500 ms, followed by a random gap period of 0–800 ms in duration, which preceded the appearance of either an eccentric target at  $20^\circ$  left or right or the reappearance of the FP at center.

**INTRUSIVE SACCADES.** To quantify the frequency of occurrence of intrusive saccades, we counted the frequency of sac-

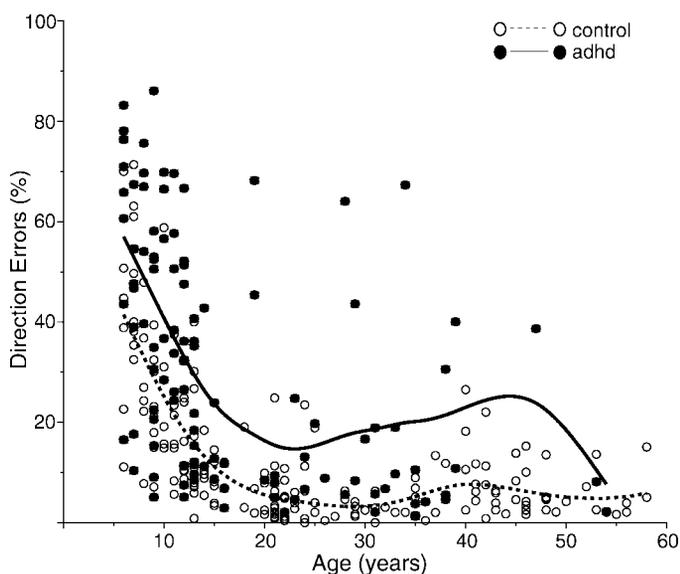


FIG. 6. Anti-saccade error rate as a function of age for control (○, ···) and ADHD (●, —) participants. Curves were fit through the data using a cubic spline function (de Boor 1978).

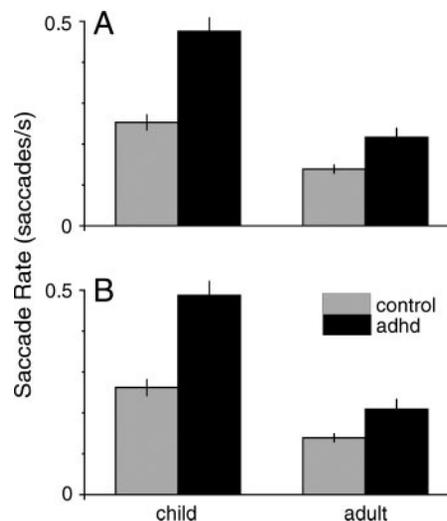


FIG. 7. Quantification of mean fixation instability for control and ADHD children and adults. Instability was measured as the rate of generation of saccades  $\geq 2^\circ$  in amplitude during instructed fixation of the visible FP (A) and the randomized gap period (B).

ades  $>2^\circ$  in amplitude that participants initiated in the final 1,000 ms of fixation on the visible FP and during the gap period. Figure 7 contrasts the mean rate of intrusive saccades during these two intervals for ADHD and control children and adults. The rate of intrusive saccades among ADHD participants was elevated above control values,  $F(1,211) = 6.06$ ,  $P = 0.01$ , and the difference in intrusive saccade rate was greater for children than for adults,  $F(1,211) = 39.76$ ,  $P < 0.001$ .

Figure 8 illustrates, in greater detail, the rate of intrusive saccades made by individual participants. The data were collapsed across the fixation and gap epochs. Both control and ADHD children showed continuous improvement (i.e., reduced frequency of intrusive saccades) across subject age. Control participants only reached adult levels of fixation stability at approximately age 16 yr. The ADHD curve lagged the control curve and appeared to asymptote at a higher level than

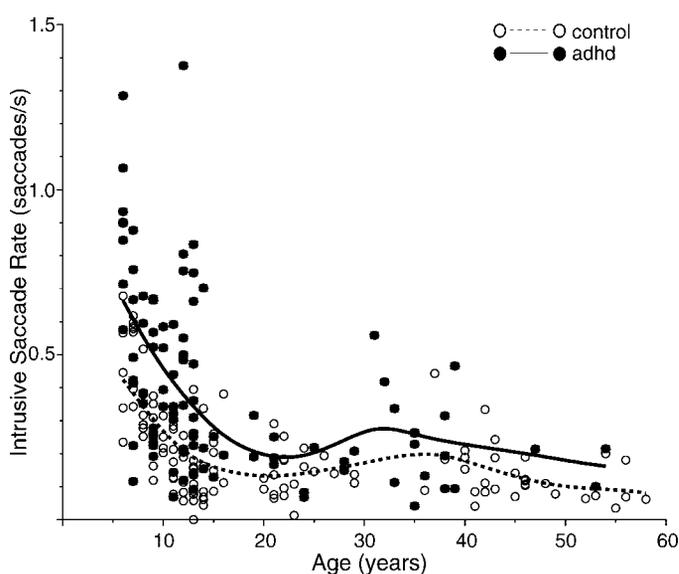


FIG. 8. Intrusive saccade rate as a function of age for control (○, ···) and ADHD (●, —) participants. Curve were fit through the data using a cubic spline function (de Boor 1978).

the control curve. Once again, note that among both children and adult groups, some ADHD participants clustered along the control curve, whereas other ADHD participants were clearly impaired, suggesting that only a subset of ADHD subjects had difficulty suppressing intrusive saccades.

**GAP EFFECT.** The gap effect reflects the exogenous component of visual fixation (i. e., difference in SRT between overlap and gap conditions). The gap effect measured from the pro- and anti-saccade tasks among ADHD and control participants was comparable,  $F(4,844) < 1$ ,  $P > 0.50$ . In the varied gap experiment, we measured mean SRT for each gap interval and compared across groups. For all groups, the longest mean SRT was obtained when the gap duration was 0 ms, the shortest mean SRT was obtained when the gap duration was 200 ms, and longer gap durations led to an increase in SRT from the minimal obtained at 200-ms gap duration,  $F(4,844) = 99.06$ ,  $P < 0.001$ . Thus it would appear that because the gap effect was comparable in all groups; the exogenous component of fixation was not impaired in ADHD.

#### Relation between anti-saccade direction errors and intrusive saccades

We have described two specific deficits in saccade suppression among ADHD participants that co-varied with subject age: a difficulty in suppressing reflexive saccades after stimulus appearance in the anti-saccade task (Fig. 6) and an inability to suppress unwanted saccades during prolonged periods of fixation (visual and nonvisual) in the randomized gap experiment (Fig. 8). These tasks were performed on separate days. Figure 9 contrasts the relationship between these two measures for each participant. Figure 9A shows the intrusive saccade rate plotted against the anti-saccade error rate for all participants. A linear regression was fit separately to the data for the control (· · ·) and ADHD (—) participants that produced significant correlation values of 0.76 and 0.60, respectively. Thus subjects with greater anti-saccade error rates were more inclined to trigger excessive intrusive saccades. Because both the anti-saccade error rate and the intrusive saccade rate co-varied with age, we recalculated the correlations after removing variability related to age effects. To perform this calculation, we subtracted the control age-matched value obtained from the cubic spline fits illustrated by the · · · in Figs. 6 and 8 from the values obtained for each subject. After removing the age-matched control values, the correlation values both remained significant but dropped to 0.46 and 0.42 for control and ADHD participants respectively (Fig. 9B).

#### DISCUSSION

We have shown that individuals diagnosed with ADHD have difficulty maintaining prolonged fixation and suppressing intrusive or unnecessary saccades. These deficits, revealed as both an increase in intrusive saccade rate (Fig. 7) and increased direction errors in the anti-saccade task in both the gap and overlap conditions (Fig. 5, *E* and *F*), compromised task performance compared with control participants. In addition, the greater variability in SRT (Figs. 3, *C* and *D*, and 5, *C* and *D*) suggests that ADHD subjects had difficulty in regulating the processes of saccade initiation. Despite these pronounced deficits in regulating the occurrence of saccades, ADHD subjects

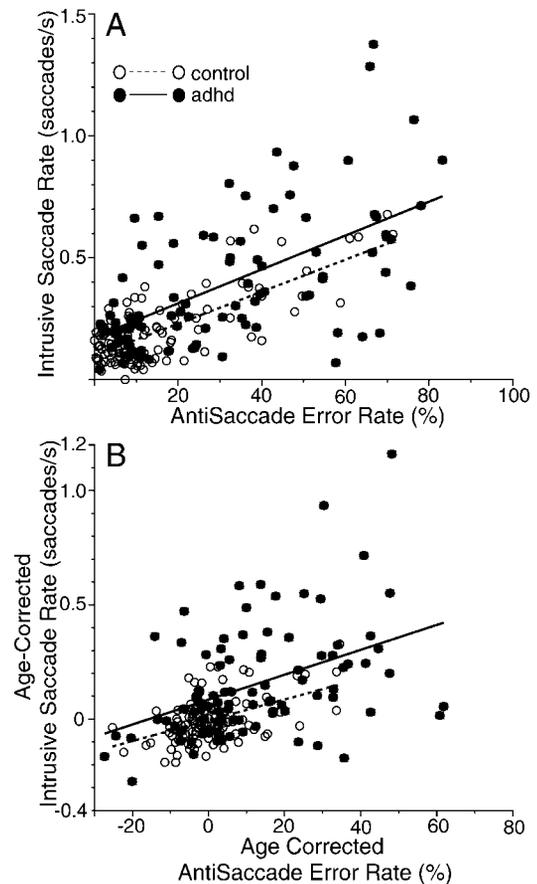


FIG. 9. A: intrusive saccade rate as a function of anti-saccade error rate for control (○, · · ·) and ADHD (●, —) participants (control line: correlation = 0.76, slope = 0.0067, intercept = 0.098; ADHD line: correlation = 0.60, slope = 0.0070, intercept = 0.17). B: intrusive saccade rate vs. anti-saccade error rate after subtracting age-matched control values (value of cubic spline fits in Figs. 7 and 9, respectively) from each subject's data (control line: correlation = 0.46, slope = 0.0045, intercept = -0.0005; ADHD line: correlation = 0.42, slope = 0.0054, intercept = 0.085).

generated saccades with normal or near-normal metrics, suggesting that the brain stem saccadic burst generator circuitry was functioning normally (Leigh and Zee 1999). We first contrast these observations with previous studies, and then we relate these findings to known neurophysiological data obtained from non-human primates performing similar tasks to speculate on the possible signals that are dysfunctional in ADHD.

#### Relation to previous studies

Our results confirm and extend previous reports describing deficits in eye-movement control in children diagnosed with ADHD. Early studies described difficulties in suppressing intrusive saccades during either visual fixation (Paus 1992; Shapira et al. 1980) or during smooth-pursuit eye movements (Bala et al. 1981; Blynsma and Pivik 1989). These earlier studies all noted an increase in the frequency of inappropriate intrusive saccades during purposive behaviors. In experiments requiring subjects to delay a saccade to a remembered target location, children diagnosed with ADHD often looked at the target location prematurely, before the go signal was provided (Mostofsky et al. 2001; Ross et al. 1994). In a recent study

employing the anti-saccade task, Mostofsky and colleagues (2001) found that ADHD children made significantly more direction errors than did age-matched control children. This result is consistent with our findings (see Fig. 5. *E* and *F*). In another study employing the anti-saccade task, Rothlind and colleagues (1991) noted modest increases in the frequency of direction errors among ADHD children that failed to reach statistical significance. However, in that study each participant performed only 10 trials in each condition, whereas we collected between 40 and 60 trials in each condition (fixation state, stimulus direction) from each participant. Another study that failed to find a difference in the proportion of correct anti-saccades between ADHD and control children using a gap anti-saccade task included a concurrent task in which participants also had to indicate the open side of a target square at the anti-location (Aman et al. 1998). Either the added task complexity or the reduced number of gap trials (42 trials vs. 80–120 in our experiments) may have accounted for this discrepancy.

The characteristics of eye movement abnormalities identified among ADHD subjects are similar to abnormalities described for patients with frontal lobe lesions. Frontal patients have difficulties suppressing reflexive pro-saccades in the anti-saccade task (Guitton et al. 1985). More recently, Gaymard and colleagues (1999) have revealed that lesions confined to the frontal eye field do not lead to increased error rates. Instead lesions to the dorsolateral prefrontal cortex, rostral to the frontal eye fields have been attributed to increased error rates on anti-saccade trials (Gaymard et al. 1998). Lesions confined to the frontal eye fields instead lead to prolonged latencies and reduced accuracy of correct pro- and anti-saccades (Rivaud et al. 1994).

Eye-movement abnormalities among patients with basal ganglia dysfunction have produced a variety of results (see Everling and Fischer 1998 for review), only some of which match the abnormalities we have reported for ADHD. Patients with Parkinson's disease, in which dopaminergic input to the striatum is reduced, have relatively normal pro-saccades, while performance on the anti-saccade task has produced contradictory results with some studies reporting no differences in reaction times and error rates (Fukushima et al. 1994; Lueck et al. 1990) and other studies finding increased reaction times and error rates (Briand et al. 1999). In Tourette's syndrome, in which it is hypothesized that the direct pathway through the basal ganglia may be overactive (Hallett 1993), patients have increased reaction times on pro- and anti-saccade tasks and no increased error rates in an immediate anti-saccade task, and instead they have a difficulty withholding saccadic responses in tasks with prolonged delay intervals (LeVasseur et al. 2001). In Huntington's disease, in which there is initial degeneration in the indirect pathway through the basal ganglia, patients produce increased direction errors on anti-saccade tasks (Lasker et al. 1987), increased reaction times (Lasker et al. 1988), and increased fixation instability (Leigh et al. 1983).

Precise control over saccade suppression is also diminished in young children (Munoz et al. 1998a); they also have difficulty suppressing reflexive pro-saccades in the anti-saccade task, have greater intra-subject variance in SRT, and generate more intrusive saccades. Task performance improves steadily in children up to the age of ~16 yr and is correlated with

maturation across a network of brain areas that includes the frontal cortex and basal ganglia (Luna et al. 2001).

An intriguing aspect of our data is the developmental progression of saccadic suppression ability in ADHD and normal participants. While our data are suggestive of a developmental delay in ADHD, some caution is warranted. The best way to investigate developmental changes in ability is to follow the same individual subjects longitudinally. In the present study, we only compared across subjects of different ages.

#### *Relation to neurophysiology*

The deficits in fixation control and saccade suppression observed among ADHD participants can be best understood in the context of recent neurophysiological studies in non-human primates that have identified neural mechanisms of fixation control, saccade suppression, and saccade production. Several brain areas are involved in the control of visual fixation and saccade production, including regions within the cerebral cortex (posterior parietal and frontal cortex), basal ganglia (caudate, substantia nigra, subthalamic nucleus), thalamus, superior colliculus, brain stem reticular formation, and cerebellum (see Hikosaka et al. 2000; Leigh and Zee 1999; Munoz et al. 2000; Scudder et al. 2002; Wurtz and Goldberg 1989 for review). Two important nodes in this network are the frontal eye fields (FEF) in the frontal lobes and the intermediate layers of the superior colliculus (SC). These structures appear to work in concert in the initiation of saccades (Munoz and Schall 2003).

Fixation neurons in the SC and FEF are tonically active during visual fixation and pause during saccades, whereas saccade neurons have a reciprocal pattern, being silent during visual fixation and active prior to and during saccade generation (Munoz and Fecteau 2002; Munoz and Schall 2003; Munoz et al. 2000). Removal of an exogenous fixation target leads to a reduction in fixation activity and disinhibition of saccade generating neurons in the FEF and SC (Dias and Bruce 1994; Dorris and Munoz 1995; Dorris et al. 1997; Everling and Munoz 2000; Everling et al. 1999). However, there is also an endogenous (nonvisual) component in the discharge of these fixation neurons (Dorris et al. 1997; Munoz and Wurtz 1993a). On anti-saccade trials, fixation activity in the SC and FEF is enhanced relative to pro-saccade trials, whereas saccade neurons in the SC and FEF are at a reduced level of excitability (Everling and Munoz 2000; Everling et al. 1999). This task-dependent modulation of fixation and saccade signals in the SC and FEF is apparent immediately after the initiation of a trial, well before the appearance of the eccentric target stimulus dictating the correct direction for a response, and represents selective control of endogenous fixation signals required to suppress reflexive or unwanted saccades.

What happens on error trials in the anti-saccade task when a non-human primate triggers a direction error and instead looks at the target stimulus? Among saccade neurons in the SC and FEF, an elevated level of pretarget activity is combined with the phasic visual response produced by the appearance of the target stimulus to trigger reflexive pro-saccades (Everling and Munoz 2000; Everling et al. 1998). Thus to correctly perform the anti-saccade task, suppression signals must be boosted to reduce the excitability of these saccade neurons. Because the location of the eccentric stimulus is varied randomly from trial to trial, successful performance on anti-saccade trials requires

inhibition of all saccade generating neurons in advance of appearance of the eccentric stimulus. The saccade neurons required to drive the correct anti-saccade are then activated only after the successful suppression of the reflexive pro-saccade. Thus the SRT for correct anti-saccades exceeds that of correct pro-saccades (see Table 2).

What are the likely sources of important endogenous control signals to the FEF and SC required for saccadic suppression? Two likely structures are the dorsolateral prefrontal cortex (DLPFC) and the substantia nigra pars reticulata (SNr). Neurons in both of these structures are modulated by voluntary tasks (Funahashi et al. 1993; Hikosaka and Wurtz 1983). The DLPFC projects directly to the FEF and SC (see Munoz and Schall 2003 for review), and this input could terminate on fixation neurons in these structures. In addition, the DLPFC and FEF project to the caudate nucleus, which contains GABAergic neurons that project directly to the SNr (see Hikosaka et al. 2000 for review). The SNr contains GABAergic neurons that project to the SC and indirectly back to the FEF via the thalamus.

The preceding pattern of connectivity is also consistent with the effects of reversible lesions in brain regions known to play a role in the endogenous control of fixation. Microinjection of the GABA<sub>A</sub> agonist muscimol into either the rostral SC (Munoz and Wurtz 1992, 1993b) or SNr (Hikosaka and Wurtz 1985) leads to artificial inhibition of important endogenous fixation signals. These experimental manipulations lead to increased frequencies of intrusive saccades and inability to suppress reflexive saccades to suddenly appearing visual stimuli, deficits that are very similar to those presented by a subset of the ADHD participants. These brain areas provide important inhibitory input to the saccade generating neurons in the SC (Hikosaka and Wurtz 1983; Munoz and Istvan 1998; Munoz and Wurtz 1993a) and possibly the FEF via a thalamic relay (Lynch et al. 1994). We hypothesize that, due to a frontostriatal pathophysiology, these suppression signals are weak or dysfunctional in ADHD.

Altered frontostriatal function could also explain the subtle but significant reduction in velocity and increase in duration of saccades in ADHD. In non-human primates, small reversible lesions of the FEFs produced with injection of lidocaine (Sommer and Tehovnik 1997) or the GABA<sub>A</sub> agonist muscimol (Dias and Segraves 1999) lead to small but significant reductions in peak saccade velocity and increases in saccade duration. Thus the slowed but accurate saccades generated by ADHD participants are consistent with altered descending input to the brain stem rather than pathophysiology affecting the brain stem and cerebellar portions of the saccadic burst generator circuitry (Leigh and Zee 1999).

### Conclusions

There are both exogenous and endogenous components of fixation control that were examined in the current study. The exogenous component of fixation appears intact in ADHD because the gap effect was normal and the occurrence of express saccades was not increased. In contrast, the ADHD group had poor control over the endogenous component of fixation that required task-dependent modulation in the diligence of fixation. This was evident from their impaired ability to suppress reflexive pro-saccades in the anti-saccade task and

intrusive saccades during periods of prolonged fixation and the increased variability in reaction times of their saccades.

We hypothesize that important saccade suppression signals related to voluntary control of endogenous fixation emanate from the prefrontal cortex and/or the basal ganglia. These signals are required to selectively inhibit saccade neurons in the FEFs and SC to control precisely the timing of saccades. Without such precise control, it is easier for the saccadic system to reach the threshold for triggering saccades. We suggest that it is the precise control of these saccade-suppression signals that is disrupted in ADHD. This lack of inhibitory control is the hallmark of the ADHD phenotype and is consistent with a frontostriatal pathophysiology. As a result, ADHD subjects have increased error rates in the anti-saccade task, increased rates of intrusive saccades, and increased intra-subject variance in SRT.

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