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RESEARCH ARTICLE

Saccadic impairments in Huntington's disease

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Abstract Huntington's disease (HD), a progressive neurological disorder involving degeneration in basal ganglia structures, leads to abnormal control of saccadic eye movements. We investigated whether saccadic impairments in HD ($N = 9$) correlated with clinical disease severity to determine the relationship between saccadic control and basal ganglia pathology. HD patients and age/sex-matched controls performed various eye movement tasks that required the execution or suppression of automatic or voluntary saccades. In the "immediate" saccade tasks, subjects were instructed to look either toward (pro-saccade) or away from (anti-saccade) a peripheral stimulus. In the "delayed" saccade tasks (pro-/anti-saccades; delayed memory-guided sequential saccades), subjects were instructed to wait for a central fixation point to disappear before initiating saccades towards or away from a peripheral stimulus that had appeared previously. In all tasks, mean saccadic reaction time was longer and more variable amongst the HD patients. On immediate anti-saccade trials, the occurrence of direction errors (pro-saccades initiated toward stimulus) was higher in the HD patients. In the delayed tasks, timing errors (eye movements made prior to the go signal) were also greater in the HD patients. The increased variability in saccadic reaction times and occurrence of errors (both timing and direction errors) were highly correlated with disease severity, as assessed with the Unified Huntington's Disease Rating Scale, suggesting that saccadic impairments worsen as the disease progresses. Thus, performance on voluntary saccade paradigms provides a sensitive indicator of disease progression in HD.

Keywords Huntington's disease · Basal ganglia · Motor control

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Introduction

Huntington's disease (HD) is a progressive neurological disorder characterized by changes in motor performance, cognitive functions, and personality (Huntington Study Group 1996). The pathophysiology underlying HD is strikingly selective, with atrophy affecting structures within the basal ganglia, most specifically the caudate and putamen (Purdon et al. 1994; Sharp and Ross 1996). The hallmark symptom of HD is the purposeless, involuntary, choreic movements seen even in the early stages of the disease (Folstein 1989; Young et al. 1986). Oculomotor impairments are also among the first manifestations of HD (Leigh

et al. 1983), probably due to the intimate involvement of the basal ganglia with the saccadic control circuit (Hikosaka et al. 2006; Hikosaka et al. 2000). Voluntary control of initiation and suppression of saccades is thought to be mediated via projections from the frontal cortex, directly to the superior colliculus (Everling and Munoz 2000; Hanes and Wurtz 2001; Segraves and Goldberg 1987) and via the basal ganglia (Hikosaka et al. 2000, 2006). Within the basal ganglia, there are two distinct pathways that output to the superior colliculus (Fig. 1a). In an intact system, the two pathways are able to work sequentially to suppress planned eye movements: the "indirect" pathway maintains inhibition on the superior colliculus suppressing the movement until a trigger to initiate a move occurs, whereas the direct pathway ramps up to selectively disinhibit the SC and produce the desired saccade (for review, see Hikosaka et al. 2000). Therefore, the "indirect" pathway through the basal ganglia may mediate saccade *suppression* via increasing GABAergic inhibitory outflow from the substantia nigra pars reticulata to the superior colliculus, whereas the "direct" pathway may mediate saccade *initiation* via decreasing GABAergic connections focally within the superior colliculus (Hikosaka et al. 2006).

The saccade system provides an excellent tool for assessing and contrasting various neurological disorders because the circuitry spans almost the entire neuraxis (Leigh and Kennard 2004; Leigh and Zee 1999; Munoz 2002). Several saccadic eye movement tasks have been developed to assess clinical populations. The *immediate pro-saccade task* is often used to test the ability to generate automatic, visually triggered saccades. In this task (Fig. 2a), subjects are required to look immediately toward a visual stimulus when it appears. This visual input to the oculomotor system arises from retino-geniculo-cortical and retinotectal pathways that can bypass both the basal ganglia and the frontal cortex. As such, automatic saccades should not be altered by the pathophysiology found in HD. However, previous studies have found deficits in the initiation of automatic saccades in HD, such as longer reaction times and increased duration of saccades (Lasker et al. 1987; Lasker and Zee 1996; Winograd-Gurvich et al. 2003).

Voluntary (goal-driven) saccades are made on command, even in the absence of an overt triggering stimulus. Examples of tasks that require voluntary saccades include the *anti-saccade task* (Fig. 2b), *delayed saccade task* (Fig. 2e), or *memory-guided sequential saccade task* (Fig. 2f). In all of these tasks, the subjects are required to first suppress a saccade toward the stimulus light when it appears, and then generate a voluntary saccade. The basal ganglia and frontal cortex are critical for voluntary saccade control (Gaymard et al. 1998; Hikosaka and Wurtz 1985b; Munoz and Everling 2004). As expected, deficits of saccadic suppression and voluntary saccade initiation have been demonstrated in HD patients (Blekher et al. 2004, 2006;

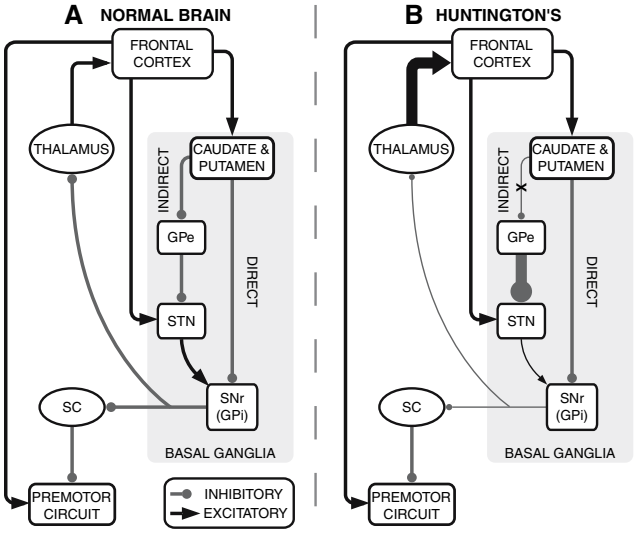

Fig. 1 Schematic of the basal ganglia (**a**) in a healthy brain versus (**b**) early stage Huntington's disease. Voluntary saccades are triggered by excitatory projections to the caudate from the frontal cortex via the indirect pathway. The CN, in turn, phasically inhibits the substantia nigra (SNr), which tonically inhibits the superior colliculus (SC). Thus, excitation of the CN could lead to disinhibition of the SC and facilitate the generation of voluntary saccades. Saccade initiation may be mediated by attenuating the inhibitory pathway to the SC via the direct pathway of the basal ganglia. *GPe/GPi* globus pallidus (external/internal); *STN* subthalamic nucleus. *Pointed arrows* denote excitatory projections, and *rounded arrows* denote inhibitory projections

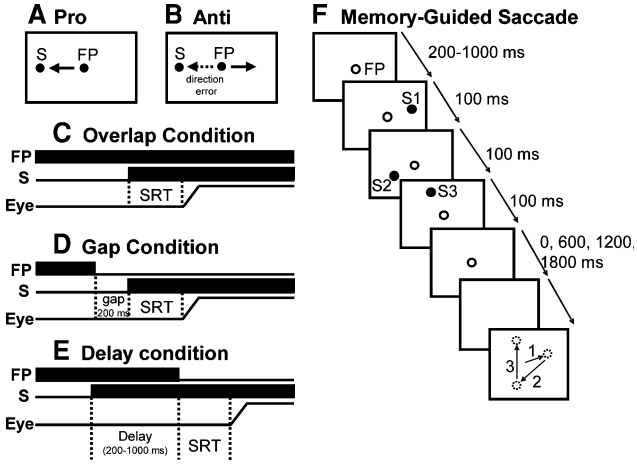

Fig. 2 Saccade paradigms: **a** Immediate pro-saccade task. **b** Immediate anti-saccade task. **c** In the overlap condition, the central FP remained on when the S appeared. **d** In the gap condition, the FP disappeared 200 ms before the appearance of the S. **e** In the delayed version of the pro-/anti-saccade task, the S appeared while the FP remained illuminated and subjects were instructed to refrain from initiating a saccade until the disappearance of FP. **f** In the delayed memory-guided sequential saccade task, three stimuli (S1, S2, S3) were presented sequentially for 100 ms each in three of the four quadrants of the visual field. The subjects were instructed to move their eyes after the disappearance of FP to the remembered location of each S in the correct order of their appearance. *FP* fixation point; *S* stimulus; *SRT* saccadic reaction time

Bollen et al. 1986; Lasker et al. 1987; Lasker and Zee 1996; Leigh et al. 1993; Tian et al. 1991; Winograd-Gurvich et al. 2003).

The motor impairments seen early in HD (O'Walker 2007) are suggestive of a problem in voluntary motor control, likely resulting from the initial degeneration of striatal efferents to the external globus pallidus (GP_e; indirect pathway) of the basal ganglia (Crossman et al. 1988; Jackson and Crossman 1984; Mitchell et al. 1989). Impairments in suppressing unwanted saccadic eye movements in the HD patients may result from reduced inhibitory outflow from the basal ganglia to the superior colliculus (Fig. 1b). As the disease progresses, the choreic movements generally tend to diminish and are replaced by increased rigidity and bradykinesia, perhaps the result of atrophy spreading to the direct pathway (globus pallidus internal (GP_i) efferents), occurring at a later stage (Storey and Beal 1993). If the direct pathway is compromised, decreased excitation from thalamus to cortex and increased inhibitory projection to the superior colliculus will likely lead to difficulties initiating saccades.

To investigate the symptomatic changes in motor control seen in early versus late stages of HD, we first examined both automatic and voluntary oculomotor behaviors. It is important to determine *how* the saccadic impairments in HD change as the disease progresses in order to further understand the patterns of atrophy in HD. We hypothesize that neural degeneration occurring in HD will lead to specific deficits in the generation of both voluntary and automatic saccades, and that these deficits will increase with worsening disease severity, possibly due to alterations in the direct and indirect pathways of the basal ganglia (Fig. 1). Clinically, changes in the pattern of deficits in saccadic eye movement tasks may provide a reliable indicator of HD progression.

Methods

Subjects

All experimental procedures were reviewed and approved by the Queen's University Human Research Ethics Board. Nine patients with Huntington's disease (HD) aged 37–69 years participated in this study, along with nine age- and sex-matched controls (Table 1). The HD subjects met clinical criteria for the diagnosis of HD based on a genetic test and were referred by a neurologist (co-author G. P.). All subjects provided informed consent and were compensated for their participation. Control and HD participants were not asked to interrupt their medications (see Table 1) during the recording sessions. Subjects wore corrective lenses if needed throughout all experiments.

HD subjects were scored on the motor and functional checklist sub-components of the Unified Huntington's Disease Rating Scale (UHDRS) to assess disease progression (Huntington Study Group 1996). The motor assessment was performed by a neurologist (co-author G. P.). The motor component has standardized ratings of oculomotor function, dysarthria, chorea, dystonia, gait, and postural stability. The total motor impairment score is the sum of all the individual motor ratings. Higher scores on the motor scale indicate more severe motor impairment. The functional assessment was carried out by an experimenter (co-author A.H). It includes a checklist regarding the subject's ability to perform common daily activities. Higher scores on the functional scale are also indicative of more severe impairment.

Experimental paradigms

The experiments were conducted in two separate 45 min sessions and were identical to those described previously (Chan et al. 2005; LeVasseur et al. 2001). In the first session, subjects performed one block of an immediate pro-saccade task (120 trials), two blocks of an immediate anti-saccade task (120 trials per block), and one block of a randomly interleaved delayed pro-/anti-saccade task (96 trials). Task instruction (pro-saccade or anti-saccade) was indicated by the color of the central fixation point (FP). In the second session, conducted 1–4 days later, the subjects performed 96 trials of a delayed memory-guided sequential saccade task. In all tasks, the subjects were given approximately 20 practice trials.

Immediate and delayed pro- and anti-saccade tasks

The subjects were seated alone in a dark room 100 cm away from a translucent visual screen. Visual stimuli consisted of red and green light emitting diodes (LEDs). The FP and peripheral stimuli were produced by LEDs (red central FP = 2.0 cd/m^2; green central FP = 1.0 cd/m^2; red peripheral stimuli = 5.0 cd/m^2). Between trials, the screen was diffusely illuminated with background illumination (1.0 cd/m^2) to reduce dark adaptation. In the immediate pro-saccade task (Fig. 2a), the subjects were instructed to look towards the peripheral stimulus as soon as it appeared. In the immediate anti-saccade task (Fig. 2b), the participants were instructed to look in the opposite direction of the stimulus as soon as it appeared. Each trial began when the background illumination was turned off and after 250 ms of complete darkness, the FP appeared. After 1,000 ms, one of two events occurred depending on the trial condition. In an "overlap" condition (Fig. 2c), the FP remained illuminated while a stimulus appeared 20° to

Table 1 Subject information

Subject	Age	Sex	UHDRS (motor/functional)	Co-morbid symptoms	Medication
Patient 1	37	Male	38/11	Depression	Atenolol (25 mg/morning); benztropine (2 mg bid); clonazepam (0.5 mg qhs); carbamazepine (400 mg tid); haloperidol (10 mg morning, 8 mg afternoon, 10 mg night); omeprazol (20 mg bid); oxybutynin (7.5 mg bid); peroxitine (20 mg/day); Ranitidine (150 mg qhs); tetrabenazine (50 mg qid)
Patient 2	37	Male	27/5	Depression	Pimozide (2 mg bid); venlafaxine (225 mg/day)
Patient 3	38	Male	12/0	–	–
Patient 4	49	Female	28/8	–	Pimozide (1 mg bid); sertraline (100 mg/day)
Patient 5	53	Male	30/12	–	Citalopram hydrobromide (40 mg qhs); olanzapine (2.5 mg qhs); tetrabenazine (25 mg tid)
Patient 6	56	Male	21/1	–	Atorvastatin (20 mg/day)
Patient 7	62	Female	42/17	–	Imipramine (10 mg qhs); pimozide (4 mg tid); tetrabenazine (25 mg tid)
Patient 8	66	Male	10/0	Depression	Atenolol (50 mg/day); atorvastatin (20 mg/day); clonazepam (0.5 mg qhs); nefazadone (100 mg tid)
Patient 9[a]	69	Female	38/12	–	Oxybutynin (5 mg tid); trazodone (5 mg qhs); risperidone (2 mg bid); sulfamethoxazole
Control 1	37	Male	–	–	–
Control 2	37	Male	–	–	–
Control 3	39	Male	–	–	–
Control 4	51	Female	–	–	–
Control 5	53	Male	–	–	–
Control 6	60	Male	–	–	–
Control 7	60	Female	–	Anxiety, depression, bipolar disorder	Imipramine (50 mg qhs); levothyroxine sodium (0.15 mg mornings); fluoxetine (30 mg morning)
Control 8	66	Male	–	Depression	Enalapril maleate (40 mg/day); hydrochlorothiazide (25 mg/day)
Control 9	69	Female	–	–	–

[a] Patient 9 did not complete the memory guided sequential saccade task

the left or right, and in a "gap" condition (Fig. 2d), the FP disappeared for 200 ms before the peripheral stimulus appeared. In both conditions, the stimulus remained illuminated for 1,000 ms, after which all LEDs were turned off and the background illumination came on for 500 ms. Stimulus location (left, right) and fixation condition (gap, overlap) were randomly interleaved within a block of trials.

In the delayed pro-/anti-saccade task (Fig. 2e) the pro- and anti-saccade trials were randomly interleaved within a block of trials. The color of the central FP provided the instruction for either a pro-saccade (red FP) or anti-saccade (green FP). The participants were instructed to delay any eye movement until the disappearance of the FP, which occurred at a randomized time (200, 400, 600, 800, or 1,000 ms) after the appearance of the stimulus. All other experimental details were in concordance with the above description.

Delayed memory-guided sequential saccade task

Eight HD subjects completed the task in session 2. Subject 9 did not return for this session. The delayed memory-guided sequential saccade task (Fig. 2f) was performed in a different laboratory and the subjects were seated 60 cm from a computer screen. Stimuli were presented on a viewSonic 17PS monitor using an S3 VGA card. The visual display had a resolution of 640 × 480 pixels, refreshed at 60 Hz. The subjects initiated the trials with a button press, and each trial subsequently began with the appearance of a central white FP on a black background. The participants were instructed to maintain fixation at the FP while three green eccentric stimuli (S1, S2, S3) were flashed sequentially in three of the four quadrants of the visual field (100 ms each with no temporal gap between stimuli). Within each quadrant, a stimulus was flashed randomly at one of 25 preset locations that were centered at 8° of visual

angle from the FP and evenly spaced within a 5 × 5 grid that ranged from 5° of visual angle at the location nearest the FP to 11° at the location farthest from the FP. The subjects were instructed to wait until the disappearance of the FP before looking at the remembered stimulus locations in the same sequence as the stimuli appeared. The interval between the disappearance of S3 and the disappearance of the FP varied randomly (0, 600, 1,200 and 1,800 ms). The sequence in which the stimuli appeared and the exact stimulus location within each quadrant varied randomly between trials, and there was an equal probability of the stimulus appearing in each quadrant.

Recording and apparatus

Immediate and delayed pro-/anti-saccade tasks

Horizontal eye movements were measured using direct current electrooculography (EOG) to obtain maximal temporal resolution. The EOG signal was amplified (Grass P18 Amplifier) and low-pass filtered (50 Hz). The horizontal eye position was digitized at a rate of 1 kHz using REX, version 5.4 (Hays et al. 1982). To calibrate, each subject was asked to direct their eyes between the left and the right peripheral stimulus locations and to the central FP. We then set the EOG amplification to 1 V = 10°. Within this range (±20°), the horizontal eye position signal remains linear (Goldring et al. 1996) and the noise remains <2°. Digitized data were stored on a hard disk and analyzed off line on a Sun Ultra 60 Spark station.

Delayed memory-guided sequential task

Eye position data were collected using a video-based eyetracker (Eyelink; SR Research Ltd, Toronto, Canada) that was mounted on the subject's head (with head movements restrained using a chin rest). The eyetracker used infrared cameras to track the movements of the pupils, measuring vertical and horizontal eye position and pupil size with a sampling rate of 240 Hz. It also provided spatial information about head position for gaze data.

Data analysis

Immediate and delayed tasks

The onset and termination of each saccade was determined when eye velocity exceeded 30°/s. The saccades were scored as correct if the first movement after the appearance of the stimulus was in the correct direction, and if it occurred after the disappearance of the FP in the delayed saccade paradigm. The saccades were classified as direction errors if the first saccade after the appearance of the stimulus was in the wrong direction and as timing errors if they occurred before disappearance of the FP in the delayed saccade paradigm. Combined timing–direction errors were classified as a third type of error.

In the immediate pro- and anti-saccade tasks, saccadic reaction time (SRT) was measured from the time of the appearance of the stimulus to the onset of the first saccade. In the delayed pro-/anti-saccade task, SRT was measured from the time of disappearance of FP to the onset of the first saccade. The saccades with SRTs <90 ms were classified as anticipatory (Munoz et al. 1998) and treated as errors. Mean SRT was computed from correct trials with latencies between 90 ms and 1,000 ms.

For every subject, the following values were computed for the immediate pro- and anti-saccade task: mean SRT for correct trials, coefficient of variation of SRT (SD/mean × 100) for correct trials, and the percentage of direction errors. Each of these measures was broken down for both gap and overlap conditions. In the delayed pro-/anti-saccade task, the percentage of timing errors and combined timing–direction errors were also measured.

Saccade metrics were analyzed for correct trials in the immediate pro-saccade task only. The average number of saccades required to reach the stimulus and the amplitude of the first saccade were calculated. Peak velocity and duration were quantified for primary saccades that fell between 18 and 21° in amplitude.

Memory-guided sequential saccade task

The Eyelink system identified saccades when peak velocities exceeded 30°/s, acceleration was greater than 9,500°/s^2 and there was motion greater than 0.15° from the position of fixation before the onset of saccade. Movement accuracy to each stimulus was measured by calculating the distance between each stimulus location and the closest eye fixation. Eye movement sequences not executed in the same order as stimulus sequences were classified as sequence errors. Eye movements occurring prior to disappearance of the FP were classified as timing errors. These movements were further analyzed to determine the direction and timing of the first saccade in which each timing error was made. The percentage of timing and sequence errors was calculated for each subject.

For all tasks, the appropriate statistical corrections for heterogeneity and sphericity of variance were made as needed (Greenhouse-Geisser). Mixed design ANOVAs were used to compare the results from all HD subjects with all age- and sex-matched controls. The variables used in all tasks to carry out the ANOVAs were subject group (HD vs. controls) and either stimulus delay (0, 600, 1,200, 1,800 ms), or stimulus location (S1, S2, S3), respectively. Correlations were made by pairing an individual HD subject with their UHDRS score, where statistical significance

was based on *t* tests different from zero. Values for right and left stimulus positions were not significantly different ($P > 0.05$), allowing the data to be collapsed across the direction for each task.

Results

Immediate pro- and anti-saccade task

Saccadic reaction time

In both pro-saccade and anti-saccade tasks, reaction times in the HD group were dramatically increased compared to controls (Fig. 3a). These findings are confirmed in the statistical analysis. Mean SRT was longer for the HD patients than for the controls across all tasks and conditions (F (1, 16) = 26.02, $P < 0.01$). Mean SRT for pro-saccades was shorter than for anti-saccades (the anti-effect (anti SRT − pro SRT); $F(1, 16) = 9.36$, $P < 0.01$); however, there was no interaction between the subject group and the experimental task ($F(1, 16) = .347$, $P = 0.56$). The anti-effect was present for both the control and the HD subjects. Mean SRTs were shorter in the gap trials than in the overlap trials (the gap effect; $F(1, 16) = 9.32$, $P < 0.01$). A planned comparison revealed that this gap effect was largely due to the control subjects in both the pro-saccade task ($t(8) = 5.539$, $P < 0.01$) and the anti-saccade task ($t(8) = 4.52$, $P < 0.01$). Among HD subjects, the gap effect was significant only in the pro-saccade task ($t(8) = 2.32$, $P < 0.05$).

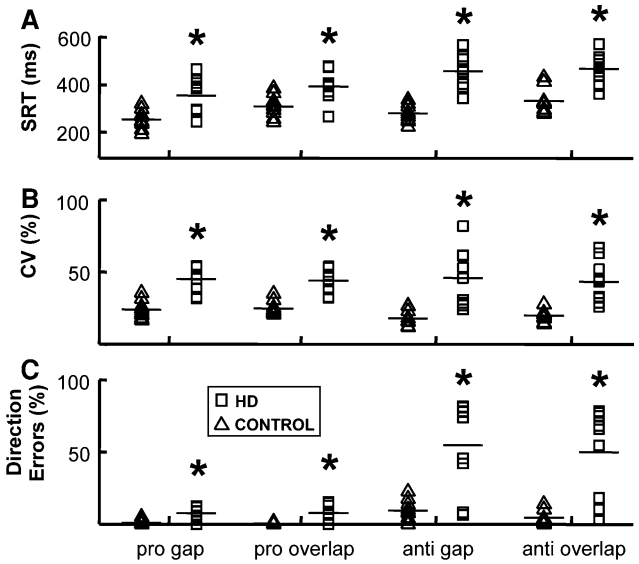

Fig. 3 Immediate pro- and anti-saccade task results in controls (*diamond*) and HD subjects (*squares*), individually plotted (*horizontal bar* mean) across task (pro-/anti) and condition (gap/overlap). **a** SRT. **b** Coefficient of variation of SRT (standard deviation/mean × 100). **c** Percent direction errors (erroneous pro-saccades). * HD:control, $P < 0.05$

Coefficient of variation

Intra-subject variability in SRT was analyzed using the coefficient of variation (CV). This measure is a unitless quantity that indicates the variability around the mean in relation to the size of the mean. CV was elevated in HD subjects compared to the controls across all tasks and conditions (Fig. 3b; $F(1, 16) = 23.73$, $P < 0.01$). In addition, HD subjects had slightly higher CV in the gap task than in the overlap task ($F(1, 16) = 13.39$, $P < 0.05$).

Direction errors

HD subjects made many more direction errors than the control subjects (Fig. 3c; $F(1, 16) = 17.45$, $P < 0.01$). More direction errors occurred in the anti-saccade task than in the pro-saccade task ($F(1, 16) = 27.07$, $P < 0.001$). Upon closer inspection, the increase in direction errors from the pro- to the anti-saccade task was considerably larger for HD subjects than for controls, resulting in a group x task interaction ($F(1, 16) = 14.83$, $P < 0.01$). Post hoc analysis indicates that in the anti-saccade task, HD subjects performed with a higher proportion of errors than the controls in both the gap ($t(9) = 3.94$, $P < 0.01$) and the overlap ($t(8) = 4.14$, $P < 0.01$) conditions.

Saccade metrics

Saccade metrics were analyzed for the immediate pro-saccade task only by comparing subject group (HD vs. control) and condition (gap vs. overlap). Measurements were based on the first saccade made after the appearance of the stimulus during correct trials only (see "Methods"). The first saccade to stimulus amongst the HD subjects was slightly smaller in amplitude (18.05° ± 0.51) compared to the control subjects (19.33° ± 0.20; $F(1, 8) = 4.77$, $P = 0.06$). There were no differences between the HD subjects (1.29 ± 0.07) and the controls (1.19 ± 0.05) in the mean number of saccades required to reach the stimulus ($F(1, 8) = 1.53$, $P > 0.2$). Among saccades that were 18–21° in amplitude, the HD subjects made saccades that were of a longer duration (134 ± 14 ms; $F(1, 8) = 9.55$, $P < 0.02$) and lower peak saccadic velocity (316 ± 26°/s; $F(1, 8) = 7.14$, $P < 0.03$) compared to the control subjects (90 ± 4 ms; 391 ± 22°/s).

Delayed pro- and anti-saccade task

Saccadic reaction time

In the delayed tasks, mean SRT was increased amongst the HD subjects when compared to the controls ($F(1, 8) = 4.89$, $P < 0.05$); however, no group x task interaction was noted.

In other words, although the HD subjects had slower SRTs than the controls, this did not vary as a function of task type, as it did in the immediate saccade task. To investigate this further, a post hoc pairwise comparison revealed that only control subjects demonstrated the anti-effect in the delayed tasks ($t(8) = 5.39$, $P = 0.001$).

Errors

There were several parameters of performance in the delayed pro- and anti-saccade tasks that were impaired in HD subjects. Figure 4a and b show that the percentage of incorrect trials was dramatically elevated in the HD patients at all delay periods, for both pro- and anti-saccades, ($F(1, 16) = 32.40$, $P < 0.001$), and the overall percentage of incorrect trials was greater in the anti-saccade trials than in the pro-saccade trials ($F(1, 8) = 6.56$, $P < 0.05$). However, in *both* the pro- and anti-saccade tasks, the number of errors increased as the delay interval increased systematically from 200–1,000 ms ($F(2, 16) = 11.28$, $P < 0.01$). In addition, HD patients made more errors in the anti-saccade task than in the pro-saccade task, a difference not observed in the controls (group x task interaction; $F(1, 16) = 8.12$, $P < 0.05$).

The errors were then segregated into three types to examine the ability of the HD patients to delay saccade responses: timing errors (saccades made in the correct direction, but before disappearance of the FP); direction errors (correctly delayed saccades, but in the wrong direction); and combined timing–direction errors (saccades made in the wrong direction before the disappearance of the FP) (Fig. 4c, d). Patients with HD made proportionally more timing errors ($F(1, 16) = 9.40$, $P < 0.01$), direction errors ($F(1, 16) = 9.33$, $P < 0.01$), and combined timing–direction errors (Fig. 4c, d; $F(1, 16) = 33.40$, $P < 0.001$). More direction errors ($F(1,16) = 9.23$, $P < 0.05$) and combined timing–direction errors ($F(1, 16) = 20.17$, $P < 0.001$) were made on anti-saccade trials, and more timing errors were made on pro-saccade trials ($F(1, 16) = 16.83$, $P < 0.01$). All types of errors were affected by delay duration in both the controls and the HD patients. More specifically, as the delay interval increased, both the percentage of timing errors ($F(2, 16) = 18.53$, $P < 0.001$) and combined timing–direction errors increased ($F(3, 16) = 9.85$, $P < 0.001$). However, the opposite relationship was observed for direction errors. As the delay interval increased, the percentage of direction errors decreased ($F(3, 16) = 20.08$, $P < 0.001$). In addition, the increase in error rate in the anti-saccade task compared to the pro-saccade task was greater for the HD subjects than for the control subjects ($F(1, 16) = 8.12$, $P < 0.05$).

Because HD patients had profound difficulty in delaying responses, we examined whether HD patients could delay their responses at *all* over long periods of time. To do this,

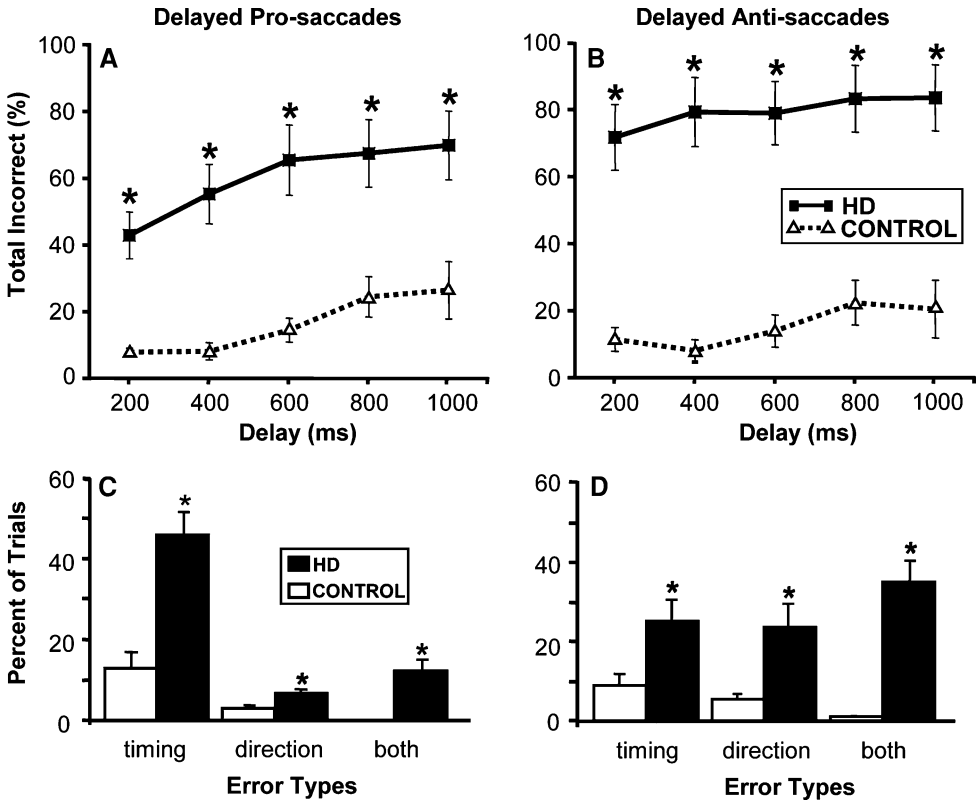

Fig. 4 Errors in the delayed pro- and anti-saccade tasks. Percentage of total errors (±standard error) in the delayed pro- (**a**) and anti-saccade (**b**) task made by HD (*square*) and control (*diamond*) subjects. Percent of trials (±standard error) in each category when broken down into correct and the three different kinds of error trials in the delayed pro- (**c**) and anti-saccade (**d**) task. * HD:control, $P < 0.05$

cumulative distributions of SRTs were constructed for both the control and the HD subjects from correct trials of the immediate pro-saccade task (overlap condition) and timing errors in the delayed pro-saccade trials in which the delay interval was greater than or equal to 600 ms (Fig. 5). In these two conditions, the stimulus display was identical: the FP and the stimulus were both visible during the 600 ms period shown and only the task instruction differed. If no timing errors were made in the delayed pro-saccade task, the cumulative distribution of SRTs in the first 600 ms of the delay period would be flat (i.e., at zero until after 600 ms). If the subjects had absolutely no ability to delay their eye movements, the curve for the delayed pro-saccade trials should be indistinguishable from that produced in the immediate pro-overlap task, where the subject was instructed to make a pro-saccade immediately upon the appearance of the stimulus. The dotted lines in Fig. 5 reveal that control subjects made nearly 100% of their saccades by 600 ms in the immediate pro-overlap task, and suppressed nearly all saccades (~90%) in the pro-delayed task until after the disappearance of FP (i.e., >600 ms). The area between the two dotted curves in Fig. 5 provides a measure of the ability of the control subjects to follow the task instruction and delay their response. The HD subjects were significantly impaired in their ability to delay, as can be seen by the much smaller shaded area between the two solid curves. Thus, although the HD subjects did have some ability to suppress eye movements until the disappearance of the FP (i.e., shaded region between the solid lines in Fig. 5), they were dramatically impaired relative to the controls.

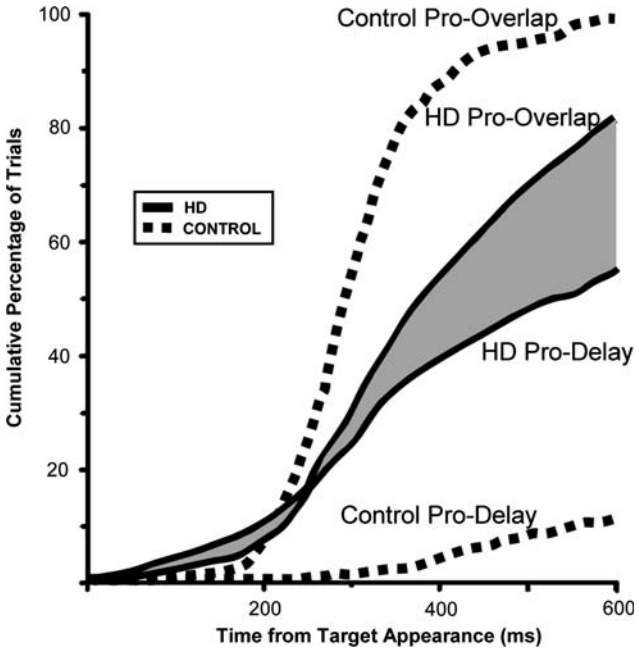

Fig. 5 Cumulative distributions of SRT in the immediate pro-overlap trials (correct responses) and the delayed pro-saccade trials (timing errors) with a delay of 600 ms of greater. *Solid lines* HD data; *dotted lines* control data

Delayed memory-guided sequential saccade task

The delayed memory-guided sequential saccade task was used to assess saccadic suppression and spatial working memory. The HD subjects produced considerably fewer correct trials than the control subjects ($t(8) = 4.463$, $P < 0.01$) in which the correct three-stimulus sequence and proper maintenance of fixation (until FP disappearance) were accomplished (Fig. 6a). The HD subjects also made more timing errors than the control subjects ($t(7) = 3.82$, $P < 0.01$). The HD patients appeared to make more sequence errors than the control subjects (not significant; $t(14) = 1.663$, $P = .12$), and did make more combined timing–sequence errors than the control subjects ($t(8) = 4.01$, $P = 0.003$).

Movement inaccuracy was assessed by calculating the visual angle between each stimulus and the closest eye fixation, and plotted as degrees of displacement from the stimulus. Among all the trials (Fig. 6b), the control subjects fixated significantly closer to the stimuli ($3.0 \pm 0.3°$) than the HD patients ($6.8 \pm 1.0°$; $F(1, 6) = 15.49$, $P < 0.01$). Similarly, the control subjects ($2.9 \pm 0.3°$) moved closer to the stimuli than the HD subjects ($6.2 \pm 0.8°$) on the subset of trials in which only correctly delayed saccades were analyzed (Fig. 6c; $F(1, 7) = 20.99$, $P < 0.01$). Finally, on the subset of trials that included only correct timing *and* correct sequence (Fig. 6d), a similar trend was observed ($F(1, 5) = 5.48$, $P = 0.07$). Note that two HD patients had zero trials in which they maintained fixation until the FP disappeared *and* carried out the correct sequence. Consequently, only six HD subjects were included in this analysis, reducing the statistical power.

Errors during the delay period may distinguish between an inability to suppress a movement to the most recently presented eccentric sensory stimulus or an inability to suppress a planned motor sequence. If subjects were unable to suppress movement to the most recently presented visual stimulus during the delay interval, then timing errors should be directed more often to the last of the successive flashes. In contrast, if subjects were unable to suppress the appropriate motor plan, the first saccade of the timing error would be directed to the location of the first stimulus. Figure 6e reveals that both the control and HD subjects tended to make their first saccade to the first stimulus (S1) more often ($F(1, 9) = 32.78$, $P < 0.001$). However, patients with HD made saccades to S1 ($48.1 \pm 4.3\%$) less often than the control subjects and then showed a gradual decline in the proportion of errors to the remaining stimuli, such that in HD, performance to S1 differed from S2 ($t(7) = 4.54$,

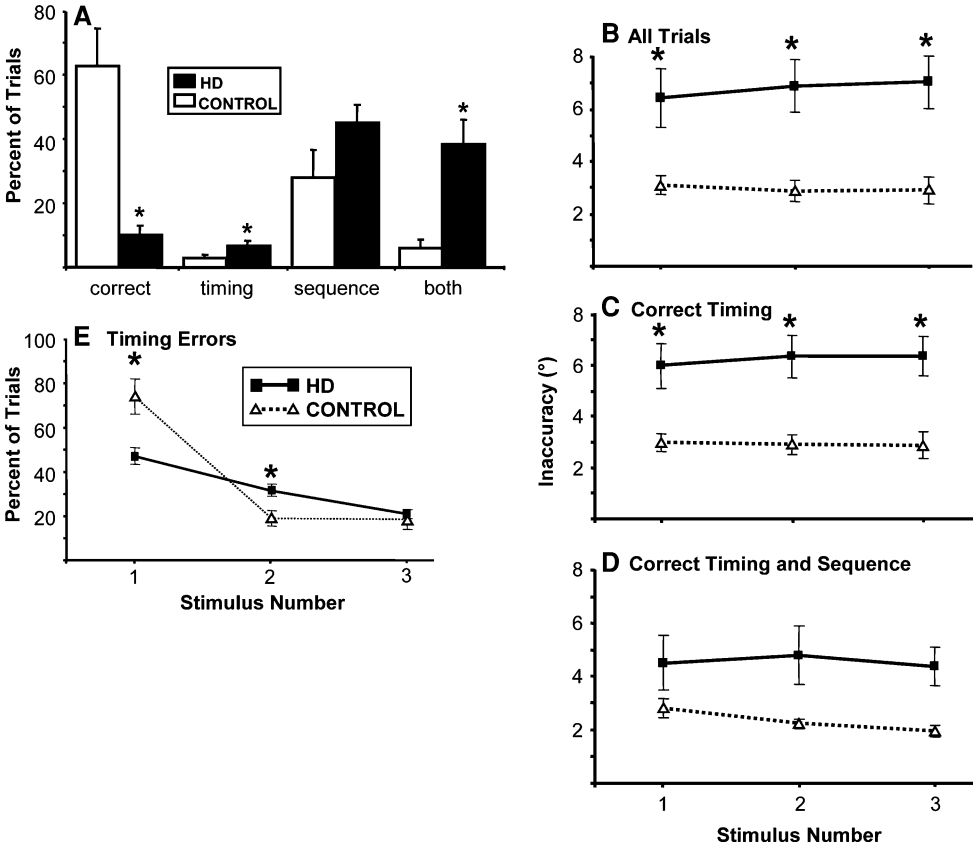

Fig. 6 Delayed memory-guided sequential saccade task results. **a** Percent of correct and incorrect trials (±standard error) for HD (*filled bars*) and control (*empty bars*) subjects. Mean inaccuracy of saccades (±standard error) to the remembered location of the first, second, and third stimuli in the sequence for (**b**) all 96 trials, (**c**) the subset of trials in which subjects did *not* make an anticipatory error (i.e., maintained proper fixation), and (**d**) those trials in which subjects maintained proper fixation *and* completed the correct sequential movement to the three stimuli. **e** Direction of the first stimulus attended when making an anticipatory timing error (i.e., percent of anticipation trials that subjects first attended each of the three stimuli (±standard error)). *Squares* HD data; *triangles* control data. * HD:control, $P < 0.05$

$P = 0.003$) and S3 ($t(7) = 4.18$, $P = 0.002$), whereas the control subjects moved to S1 significantly more (71.1 ± 8.5%) than to S2 or S3, with no difference of probability of movement between these latter points ($F(1, 8) = 9.49$, $P < 0.01$). This suggests that timing errors resulted from a failure to suppress a planned motor program. Confirming this, no difference was observed between the mean SRT of the control and the HD subjects ($F(1, 8) = 0.21$, $P > 0.5$), or between the mean SRT of saccades to each of the three stimuli ($F(2, 21) = 0.44$, $P = 0.65$).

Correlations to disease severity

Identification of a simple behavioral measure that correlates with disease progression may be useful to track clinical changes in HD patients and to predict pre-symptomatic disease onset. Several of the saccadic parameters we measured correlated with measures of disease severity (Table 2), as assessed by motor and functional subcomponents of the UHDRS (see "Methods"). Figure 7b and d illustrates that as the severity of the disease worsened, HD subjects showed more variability in their SRTs (Table 2, $P < 0.01$). The frequency of direction errors correlated with disease severity in both the immediate pro- ($P < 0.05$) and anti-saccade tasks (Fig. 7a, c and Table 2; $P < 0.01$). In the delayed anti-

Table 2 Correlations (Pearson r values) between various measures of saccadic behaviors and motor and functional assessment scores in individuals with HD

	Motor		Functional	
	Pro	Anti	Pro	Anti
Immediate pro- and anti-saccade task				
Latency	0.219	0.147	0.298	−0.049
Percent direction error	0.617	0.923**	0.543	0.870*
CV	0.861**	0.890**	0.745**	0.876*
Delayed pro- and anti-saccade task				
Latency	0.359	0.415	0.303	0.439
Percent timing errors	0.071	−0.486	0.169	0.033
Percent direction errors	0.429	0.111	0.573	0.033
Percent combined	0.556	0.930**	0.471	0.810*
Delayed memory-guided sequential saccade task				
Percent correct	0.359	0.415	0.303	0.438
Total % errors	0.556	0.930**	0.471	0.810*
Saccade metrics	Pro		Pro	
Amplitude	0.748*		−0.536	
Duration	0.678*		0.563	
Velocity	0.409		0.508	

* $P < 0.05$

** $P < 0.01$

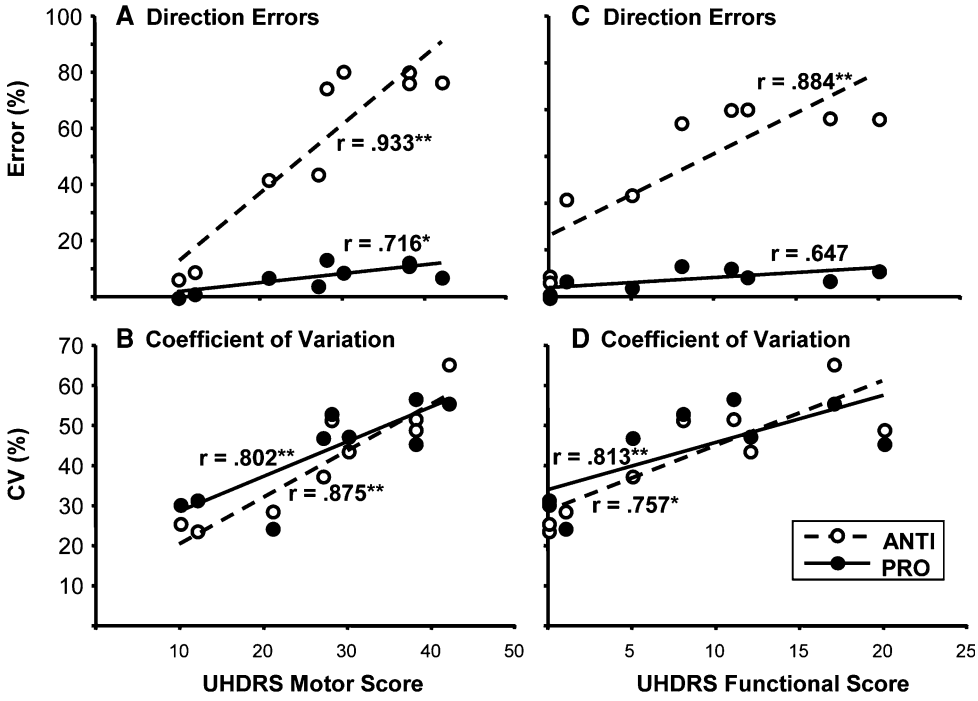

Fig. 7 Mean correlations between saccade measures and disease severity in HD subjects, as assessed by the Unified Huntington's Disease Rating Scale (UHDRS). Direction errors (**a**, **c**) and coefficient of variation (**b**, **d**) correlating with the motor (**a**, **b**) and functional scores (**c**, **d**) of the UHDRS are shown for both the pro-saccade task (*solid lines*), and the anti-saccade task (*dashed lines*). See Table 2 for values

saccade task, the rate of combined timing–direction errors strongly correlated with disease severity (Table 2; $P < 0.01$). In the delayed memory-guided saccade task, the percentage of total errors increased with disease severity (Table 2); however, the accuracy reaching the stimuli did not correlate with disease progression (Table 2, $P < 0.05$). Of the saccade metrics, saccade amplitude and duration in HD subjects were correlated with disease severity (Table 2, $P < 0.05$). Mean SRT in HD subjects did not correlate with disease severity, regardless of the task (Table 2, $P > 0.05$).

Discussion

We examined impairments in saccadic eye movements amongst individuals with HD and identified multiple deficits in automatic and voluntary saccade control. Consistent with previous studies (Blekher et al. 2004; Blekher et al. 2006; Lasker et al. 1987; Leigh et al. 1983; Tian et al. 1991), we have confirmed that HD subjects have the following eye movement abnormalities: (1) Difficulties initiating voluntary saccades, identified as increased SRT in the immediate (Fig. 4) and delayed pro- and anti-saccade tasks**.** (2) Reduced ability to suppress inappropriate automatic saccades (Figs. 3, 4, 5, 6). (3) An inability to hold and execute complex motor plans involving spatial working memory (Fig. 6). (4) Atypical saccade metrics. (5) Correlations between voluntary saccade measures and HD disease severity (Fig. 7). We discuss the implications of these findings in relation to known pathophysiology in the HD patients and their relation to disease severity.

Relation to brain pathology

Based on the evidence presented above, the view commonly held that HD is a disorder involving primarily the indirect pathway of the basal ganglia (i.e., the pathway responsible for suppressing saccades; see Fig. 1b) is incomplete. Although previous research has suggested that most of the atrophy in HD is localized to the indirect pathway (Albin et al. 1990; Johnson et al. 2001; Reiner et al. 1998; Vonsattel et al. 1985), with relative sparing of the direct pathway (i.e., damage to which would likely result in increased inhibition to the superior colliculus and difficulty initiating/generating saccades), the results from the present study, along with anatomical and physiological evidence (Storey and Beal 1993), suggest that this differentiation of the pathology is an oversimplification of the circuit. In its later stages, HD may also be associated with cell loss in areas that receive basal ganglia outputs, including the thalamus, subthalamic nucleus, substantia nigra, cerebellum, cortex, and brainstem (Johnson et al. 2001; Kassubek et al. 2005; Macmillan and Quarrel 1996). We have shown deficits in tasks requiring the generation of *both* automatic and voluntary saccades, albeit *greater* deficits seen in tasks requiring saccadic suppression (e.g., anti-saccades, delayed saccades, and memory-guided saccades—all of which elicited performance changes correlated with disease severity). Considering that suppression deficits correlate with disease severity (Fig. 7, Table 2), and initiation deficits do not (Table 2), it can be inferred that the areas in the basal ganglia involved in suppressing unwanted saccades are more susceptible to the pathological changes that occur as the

disease severity worsens. This parallels other findings (Blekher et al. 2006) wherein similar anti-saccade and memory-guided saccade tasks were most effective in differentiating impairments in pre-diagnostic HD gene carriers versus nongene carriers. However, the memory-guided saccade task that we employed required subjects to remember the location of three stimuli that could appear anywhere within three of the four visual quadrants (each with 25 different locations), a task more challenging than those previously employed (Blekher et al. 2006; Lasker et al. 1987, 1988). Consequently, deficits were much more pronounced; recall that two HD patients were unable to perform a single correct trial. Taken together, our findings support prior pathophysiological findings, which suggest that although the striatal-globus pallidus (external) portion of the indirect pathway in the basal ganglia is where degeneration initially occurs, the direct pathway is also compromised in HD, perhaps at a later stage of disease progression (Albin et al. 1990; Berardelli et al. 1999; Storey and Beal 1993). Both localized and widespread cell loss in HD patients would eventually lead to deficits in the generation of both automatic and voluntary saccades, as demonstrated in this study.

The pattern of neural degeneration in HD and how it affects saccadic control can be summarized as follows. First, supporting evidence from electrophysiological and lesion studies suggests that the frontal (Everling and Munoz 2000; Gaymard et al. 1998) and supplementary (Amador et al. 2004) eye fields play an important role in the execution of voluntary saccades, both of which have projections through the basal ganglia. Therefore, we would expect that altered input to one or all of these structures would make it more difficult to excite the superior colliculus and initiate a voluntary saccade. Secondly, it is suggested that frontal lesions may be implicated in saccade initiation deficits (Tian et al. 1991), or that abnormalities in the substantia nigra (pars reticulata), superior colliculus, or the brainstem itself cause the elevated latencies in automatic saccades (Hikosaka and Wurtz 1985a, 1985b). Reduced excitability from the direct pathway of the basal ganglia to the saccade generating circuit (via compromised frontal structures) could lead to reduced ability to initiate movement. Alternatively, increased sensory-processing delays are also known to occur in the HD subjects (as assessed by auditory and visual event-related potentials (Goodin and Aminoff 1992)), which may also slow saccadic reaction times. Thirdly, the prefrontal cortex has been implicated in executive functions such as spatial working memory (Miller and Cohen 2001), and is critical for suppression of erroneous automatic saccades in the anti-saccade task (Condy et al. 2007; Guitton et al. 1985; Pierrot-Deseilligny et al. 1991). Damage to the frontal cortex may also lead to decreased inhibition of the superior colliculus (via the basal ganglia or the direct projection from the cortex to the subthalamic nucleus (Hikosaka et al. 2000)), which can influence saccadic control (i.e., intra-subject variability), and the ability to generate and execute a correct motor plan (via a global over-excitation of the saccade-generating circuit). Finally, changes in saccade metrics can also be accounted for by changes occurring in the basal ganglia and the frontal cortex. Control of saccade amplitude has been associated with a feedback loop through the basal ganglia to the superior colliculus (Kimmig et al. 2002), which is perhaps responsible for the decreased amplitude in saccades of patients with Parkinson's disease (Chan et al. 2005). However, the specific pattern of degeneration in the basal ganglia of HD patients instead influenced the velocity and duration of saccades. This region-specific atrophy in the basal ganglia and frontal cortex may account for the progressively more hypometric saccades seen in HD patients as the disease progresses. In addition, slowed saccade velocities are often attributed to abnormalities in the brainstem reticular formation (Leigh and Zee 1999; Scudder et al. 2002). Slowed saccades are also found in patients with lesions of the frontal eye fields and the superior colliculus (Gaymard et al. 1998; Pierrot-Deseilligny et al. 1991), and monkeys with reversible inactivation of the frontal eye fields (Dias and Segraves 1999; Sommer and Tehovnik 1999) and superior colliculus (Hikosaka and Wurtz 1985; Lee et al. 1988), the major inputs to the premotor circuit in the brainstem reticular formation (Munoz 2002).

Relation to disease severity

Detection of a simple behavioral measure that correlates with functional disease progression is important to track clinical changes in HD patients and could be used as a tool in controlled clinical trials to assess improvements in motor and functional abilities during therapeutic interventions. Eye movement deficits were correlated to motor and functional capacities of HD patients, as assessed by the UHDRS (Table 2). A decline in the HD subject's ability to perform these saccadic eye movement tasks can provide an important index of disease progression. Most of these progressive deficits observed in HD can be linked to degeneration of the basal ganglia and the frontal lobes (Berardelli et al. 1999; Tsai et al. 1995). The ability of subjects with HD to *suppress* saccadic eye movements progressively worsened with the degree of disease severity (Table 2, Fig. 7) suggesting a more rapidly advancing neural degeneration in the *indirect* (inhibitory) pathway of the basal ganglia and frontal cortex over the course of the disease that directly affects saccadic suppression. This is due to alterations in basal ganglia modulation (i.e., striatal atrophy leading to increased excitation to frontal cortex (via thalamus) and decreased tonic inhibitory outflow to the superior collicu-

lus; see Fig. 1b). This implies that worsening voluntary saccadic dysfunction provides insight into the spreading pathophysiology.

A further, perhaps speculative, implication of these findings is that because neural degeneration in HD begins in the basal ganglia, and saccadic suppression appears to be affected directly by these changes, measures of saccadic suppression, specifically, may be an effective *early indicator* of disease onset in pre-symptomatic HD patients. Comparable studies (Blekher et al. 2006; Smith et al. 2000) observed that fully diagnosed HD patients were more severely impaired than pre-symptomatic HD gene carriers, who were more impaired than controls in measures of movement control (oculomotor and reaching, respectively), which are findings similar to our study. Recall that certain oculomotor impairments that we found (inability to suppress incorrect automatic saccades and drastically reduced precision and accuracy) changed with disease severity, supporting that by the time of diagnosis, the associated neuronal degeneration had already advanced (Aylward et al. 2004). Therefore, eye movement testing, the *immediate anti-saccade task* in particular, may prove to be a useful early marker of symptomatic disease onset in HD.

Although many of the observations discussed above involve the basal ganglia and/or the frontal cortex, we cannot be sure that these deficits solely reflect dysfunction in these structures due to the complex involvement and interaction of other brain structures in HD, many of which also experience cell loss in the later stages of the disease. However, understanding the progressive changes in oculomotor behavior may provide future insight into the neural pathophysiology in HD. Since worsening saccade performance provides a strong indicator of disease severity in HD, saccadic eye movements could be a useful and sensitive clinical tool in assessing motor and functional changes in individuals with HD.

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