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Saccades in Huntington’s disease: Predictive tracking and interaction between release of fixation and initiation of saccades

J.R. Tian, MD; D.S. Zee, MD; A.G. Lasker, MS; and S.E. Folstein, MD

Article abstract—We compared saccadic eye movements in 21 patients with Huntington’s disease (HD) and 21 normal subjects. In a predictive tracking task, HD patients were unable to anticipate normally the timing and location of a visual target that alternated its position predictably (± 10°, 0.5 Hz; mean latency of +170 msec in HD and −78 msec in normal subjects). HD patients and normal subjects, however, showed comparable decreases in saccade latency (110 msec in HD, 124 msec in normal subjects) when the fixation target was turned off 200 msec before (gap task) versus 200 msec after (overlap task) the appearance of an unexpected peripheral stimulus. Taken together, these findings support the idea that HD patients show greater defects in initiating internally generated than in initiating externally triggered saccades. This dichotomy is likely due to involvement of frontal lobe—basal ganglia structures in HD, with relative sparing of parietal—superior collicular pathways.

Huntington’s disease (HD) is a hereditary, degenerative disorder in which certain structures within the basal ganglia related to eye movement control—the caudate nucleus (CN) and the substantia nigra pars reticulata (SNpr)—are prominently involved.12 The latter structure influences saccades by virtue of its projections to the superior colliculus (SC). Abnormalities of eye movements have long been recognized in HD; slow saccades and difficulty in initiating saccades are clinically the most conspicuous findings.3 Recent studies, using quantitative recordings of eye movements and testing paradigms designed to probe higher-level control of saccades, have revealed a characteristic pattern of disorder.4–7 Patients show excessive “distractibility”; that is, they have difficulty in suppressing a saccade to a suddenly appearing visual stimulus when instructed to maintain straight-ahead fixation or when instructed to make a saccade in the direction opposite to the target (the “antisaccade” task). Furthermore, patients show an increase in latency that is greater for saccades on command (“volitional” saccades) than for saccades made to unexpected stimuli (“reflexive” saccades).

These abnormalities in HD have been attributed to involvement of the frontal lobes or the basal ganglia since these structures are thought to be important in the generation of more volitional, internally generated saccades in the context of learned, remembered, or anticipated behavior.8–10 In contrast, more posterior cortical structures, via direct projections to the SC, are thought to be more concerned with generating reflexive, externally triggered saccades to the unexpected appearance of visual stimuli. This pathway is thought to be relatively spared in HD.

With this dichotomy between voluntary and reflexive control in mind, we further investigated saccades in patients with HD. We examined the ability to generate volitional saccades that anticipate the location of a target moving in a predictable fashion (with respect to both timing and location). We also investigated the influence of the early removal (the “gap” task) or of the persistence (the “overlap” task) of the fixation target upon the time to initiate reflexive saccades to a target that appeared unexpectedly.11 Normally, saccade latencies are increased in the overlap and decreased in the gap paradigms.

Methods. General procedures and eye movement recordings. The subjects sat in front of an arc (radius, 123 cm) within which an array of light-emitting diodes (LEDs) were located at 0°, and at right and left 10°, 20°, and 30°. Head movements were restricted by the use of a chin rest. Except for the LEDs, all recordings were performed in complete darkness. Movements of the right eye were recorded with direct-current electro-oculography, low-pass filtered (40 Hz), and digitized and saved at a rate of 100 Hz by an LSI 11/73 microcomputer. The computer also controlled the target presentations.

Testing paradigms. Seven testing paradigms were used: three designed to elicit reflexive saccades; one designed to test the suppression of reflexive saccades; and three designed to elicit volitional, predictive saccades.

For the three reflexive saccade paradigms and the one suppression paradigm, each trial began with the illumination of an LED located straight ahead, at 0°. At a random time...
(1,400 to 2,400 msec), direction (right and left), and amplitude (10, 20, or 30 degrees), one of the six peripherally located LEDs was illuminated. Sixty trials were elicited for each paradigm. All subjects were instructed to "quickly move your eyes to the target."

Paradigm NS (novel stimulus). The central fixation LED was extinguished simultaneously with the onset of the peripheral target LED. This paradigm tested the subject's ability to initiate saccades to a suddenly appearing, unpredictable visual stimulus.

Paradigm OS (overlap stimulus). The central fixation LED was extinguished 200 msec after the onset of a peripheral target LED. This paradigm tested the effect of persistence of the central fixation target upon saccade latency.

Paradigm GS (gap stimulus). The central fixation LED was extinguished 200 msec before the onset of a peripheral target LED. This paradigm tested the effect of early removal of the central fixation target upon saccade latency.

Paradigm MS (mirror stimulus or antisaccade task) was used to test for suppression of reflexive saccades. The central fixation LED was extinguished simultaneously with the onset of a peripheral target LED. The subject, however, was instructed to look in the direction opposite to the target, at its mirror location in the opposite visual field. An LED was illuminated in the mirror location 750 msec later so that the subject could make, if necessary, a corrective saccade to the target.

The predictive paradigms called for saccades to be made back and forth between targets located at ±10° at a frequency of 0.5 Hz. Each predictive paradigm consisted of 25 trials.

Paradigm PL: the lights were alternated.

Paradigm PB: a nonlocalizable beep (100 msec) was sounded simultaneously with each target jump.

Paradigm PS: the right and left diodes were both continuously illuminated while the beep was sounded at a frequency of 0.5 Hz.

In paradigms PL and PB, the subjects were instructed to "move your eyes in time with the target." In paradigm PS, the subjects were instructed to "move your eyes in time with the beep."

Data analysis. Data from each individual trial were displayed on a video monitor. Maximum saccadic velocities, amplitudes, and latencies were determined by using an interactive computer analysis program that displayed each trial for review by the experimenter. The experimenter was able to verify the computer's determination of the beginning and the end of a saccade. All saccades with latencies ≤100 msec were judged to be anticipatory saccades. In the nonpredictable paradigms, any saccade with a latency greater than 3 SDs from the mean of all saccades elicited in that paradigm was removed. For predictive saccades, analysis was performed by hand on chart recorder paper at a speed of 50 mm/sec. In the MS (antisaccade) paradigm, the percentage of errors (saccades made toward, instead of away from, the visual stimulus) was determined. Statistical analyses were performed with the Student's t-test, linear regression analysis, chi-square test, and a test for whether or not a distribution is Gaussian. The criterion for significance was p < 0.01.

Patients. Twenty-one patients with HD and 21 normal subjects were investigated. The patients with HD were minimally to mildly affected with respect to both cognitive and motor performance. Cognitive capabilities were assessed with the Mini-Mental State test (MMS) and motor performance with a quantitative neurological examination battery (QNE). Eight patients were below the normal range of 24 to 30 in MMS, whereas all of the patients were abnormal in the QNE. Symptoms appeared in six patients before the age of 30 years. Sixteen of 21 patients took some type of medication, although there were still abnormalities on the predictive tracking task in 75% of the patients who took no medications at all. The patients' ages ranged from 23 to 62 years (42.7 ± 12.4), normal subjects' from 19 to 63 years (39.4 ± 12.6).

Results. Reflexive saccades (NS paradigm). Mean latencies to saccade initiation in the reflexive saccade paradigm were slightly but significantly (p < 0.01) increased in patients with HD. Values were 327 msec in HD and 245 msec in normal subjects (table 1A). There was a small, but not statistically significant, difference in amplitude of saccades in the reflexive paradigm. For 20° target displacements, the mean amplitude was 17.2° (SD, 3°) in HD patients and 18.6° (SD, 0.8°) in the normal group. Saccades were slow in eight of 21 HD patients using as a criterion of abnormality a mean peak velocity for 20° saccades of less than 243°/sec (2 SDs below the mean for the normal subjects). We found no correlation between the values of the mean or SD of saccade latency and age in either the patient or the normal group.

For both saccade latency and amplitude, HD patients showed a statistically significant (p < 0.01) increase in the amount of individual variability. For latencies, the mean value of the individual SDs was 113.2 msec (SD, 57.8) in the HD group and 57.9 msec (SD, 22.3) in the normal group. For amplitude (20° target displacements), the mean value of the individual SDs was 4.1° (SD, 1.6) in the HD group and 1.8° (SD, 1.0) in the normal group.

For each subject, we also examined the distribution of the individual measures of saccade latencies and of
the values of the reciprocal of saccade latencies. Testing for a Gaussian distribution,\textsuperscript{12} we could not show any statistically significant differences between the normal and HD groups, either for saccade latencies or for the reciprocal of saccade latencies. For both HD and normal subjects, more individuals had distributions that were Gaussian when the reciprocal of latency rather than when the latency itself was analyzed (11 versus 4 in HD patients, and 12 versus 4 in normal subjects).

\textit{Gap and overlap paradigms}. To examine the effects of changing the timing between the offset of the fixation target and the onset of the peripheral target on reflexive saccades, we compared saccade latencies in the gap (GS), overlap (OS), and reflexive (NS) paradigms (table 1A). There was a significant difference between the HD and normal groups in the latencies for the NS and GS paradigms. There were no significant differences between the two groups, however, in the amount by which latencies were changed when the timing characteristics between the offset of the fixation target and the onset of the peripheral target were altered (table 1B). The mean difference in latency between the gap and the overlap paradigms was 124.5 msec in the normal group and 109.9 msec in the HD group.

\textit{Suppression of reflexive saccades}. We examined the ability of patients to suppress a reflexive saccade to a visual target when instructed to look in the opposite direction. All patients with HD showed an abnormal number of incorrect responses using 30\% or more as a criterion for abnormality (mean + 2 SDs in the normal group). The mean value for HD patients was 68\% (SD, 17). Only one subject from the normal group showed an abnormal score (32\%).

\textit{Predictive paradigms}. Typical responses in the predictive tracking tasks (for example, the PL paradigm, light cue only) for one normal subject and for one patient are shown in figure 1, A and B. Note the overall higher value of saccade latencies and the lower number of saccades that were anticipatory (5100 msec before the target jumped). In each figure, the thick solid line indicates the mean value of latencies for reflexive saccades (NS paradigm) in the subject.

Figure 1. Prediction in a normal subject (A) and in an HD patient (B). PL paradigm (LEDs illuminated alternately [0.5 Hz] at right and left 10 degrees). Latencies for rightward and leftward saccades are plotted separately, for 25 consecutive cycles. Negative latency indicates saccade was initiated before the target jumped. In each figure, the thick solid line indicates the mean value of latencies for reflexive saccades (NS paradigm) in the subject.

Figure 2. Mean value of saccade latency for each individual subject in PL paradigm (pl, light cue only). Negative latency indicates that saccades were initiated before the target jumped. Note the difference between the values for saccade latency in the normal and the HD groups.
abnormality, 15 of 20 HD patients, but only one of the normal group, were outside the normal range. For PL minus NS, 13 of 20 HD patients and no normal subjects were outside the normal range. For both PL, and PL minus NS, the differences between groups were statistically significant (chi-square, p < 0.01). Mean saccade latencies for all three predictive paradigms as well as the PL minus NS values are summarized in table 2A. In each instance, latencies were greater in the HD than in the normal subjects.

When comparing the values of the differences between the latencies in the predictive paradigms—PL (light cue) minus PS (sound cue); PB (light and sound cue) minus PS; and PL minus PB—there were no significant differences (at the p < 0.01 level) between the HD and the normal groups (table 2B). Thus, while HD patients showed a significant defect in their ability to decrease saccade initiation time in the predictive paradigms, there was no significant difference in the amount by which added auditory cues could lead to a further decrease in saccade latency.

Within each group, however, there were significant differences between the values in the different predictive paradigms (table 2A). For HD patients, each value was significantly different from each other (p < 0.01, paired t test). In the normal subjects, the value for the PS paradigm was also significantly different from the value in the PL and in the PB paradigms, but the PL and the PB values were not significantly different from each other (table 2A).

We also determined the percentage and the amplitude of saccades that were anticipatory in each of the predictive paradigms (table 3). An anticipatory saccade was defined as being initiated ≤100 msec following the target jump. In each instance, HD patients showed a significantly lower percentage of anticipatory saccades. Using a criterion for abnormality of greater than 2 SDs from the mean value of the normal group, a majority of HD patients were abnormal (13 or 14 of 20, depending on the paradigm [table 3]), whereas only one or none of the normal subjects was abnormal. For the amplitude of anticipatory saccades made in the predictive paradigm (PL), HD patients but not the normal subjects showed a significant decrease (p < 0.01) from the value in the reflexive (NS) paradigm. For normals, the mean amplitude was 17.8° (the value in the NS paradigm was 18.6°) while for HD patients the mean amplitude was 14.2° (the value in the NS paradigm was 17.2°). Likewise, HD patients had a significant difference (p < 0.01) from normals in the variability of the amplitude of antici-
The importance of the SC in the generation of saccades is supported by the observation in monkeys that acute lesions of the SC impair their ability to make any type of saccade. After ablation of the SC, however, animals do recover the ability to generate saccades (mean value of SD of 2.2° in normal subjects and 3.2° in HD patients).

Discussion. Before attempting to interpret the specific results of our experiments, we will present a hypothetical scheme of how the frontal and the parietal lobes, the basal ganglia, and the superior colliculus (SC) in the generation of saccades. Parietal—SC pathways presumably trigger reflexive saccades. Voluntary saccades are triggered from the frontal lobes by direct excitatory projections to the SC, by excitatory projections to the caudate nucleus (CN), or both. The CN, in turn, phasically inhibits the substantia nigra pars reticulata (SNPr) which itself tonically inhibits the SC. Thus, excitation of CN could lead to disinhibition of the SC and facilitate the generation of voluntary saccades. Suppression of uncalled for reflexive saccades could occur via frontal cortex by a direct inhibitory pathway to the SC or indirectly by an inhibitory pathway to CN. The dashed line indicates a direct frontal—brainstem pathway that probably triggers saccades when the SC is removed. FEF = frontal eye fields; SEF = supplementary eye fields; LIP = lateral intraparietal area.

In intact subjects, more reflexive saccades are probably triggered via direct projections from the parietal lobes to the SC. More voluntary saccades are probably generated from frontal structures, either directly, or via the basal ganglia, to the SC. The CN and the SNPr are presumably the structures in the basal ganglia that influence saccade generation by the SC. More specifically, the SNPr, by a tonic inhibitory influence upon the SC, probably gates reflexive and volitional saccades that are generated by the SC. The CN, by an inhibitory projection to SNPr, can phasically inhibit SNPr and thereby lead to disinhibition of the SC and "permit" a saccade to occur. A projection from the frontal lobes to the CN presumably carries the signal that phasically excites caudate neurons and leads to inhibition in the SNPr and then facilitation of the generation of a voluntary saccade. At other times, the SNPr tonically inhibits the SC and prevents uncalled for, reflexive saccades.

There are, however, other potential ways by which reflexive and voluntary saccades could be gated through the SC (figure 4). There are direct projections from frontal structures to the SC, some of which could trigger voluntary saccades and others could suppress reflexive saccades. There might also be inhibitory projections from the frontal lobes to the CN which could serve, in effect, to increase SNPr inhibition upon the SC and help prevent uncalled for saccades.

It must be emphasized that the frontal and parietal lobes are reciprocally connected, allowing for each structure to influence the other, and have common subcortical projection sites. This anatomic complexity precludes a strict separation of function between the posited voluntary and reflexive pathways for initiation of saccades. Nevertheless, we will use the scheme outlined in figure 4 to analyze the findings shown by our patients.

Reflexive saccades in HD. The changes in reflexive saccades shown by our patients with HD were similar to those reported previously. There was a mild increase in saccade latency but no statistically significant difference in amplitude. There was, however, a considerable increase in the amount of intrasubject variability, in both amplitude and latency, in the HD group. We could not, however, distinguish normal subjects from HD patients on the basis of whether or not, in a given individual, the distribution of saccade latencies, or the distribution of the reciprocal of saccade latencies, was Gaussian. Likewise, as reported previously in normal subjects, both our patient and normal groups contained more subjects with a Gaussian distribution when the reciprocal of saccade latency was analyzed.

The pathophysiology of the abnormalities of the initiation of reflexive saccades in patients with HD is not known. Increases in latency for reflexive saccades are usually associated with parietal lesions, although in other reports, frontal lesions, too, have been implicated. Abnormalities in the SNPr, SC, or the brainstem itself could be other explanations for an increase in reflexive saccade latency.

Abnormalities in suppression of reflexive saccades. As shown before, impaired suppression of reflexive saccades (ie, excessive distractibility) was demonstrated by all of our patients on the antisaccade task. The excessive distractibility in HD has been attributed to a loss of tonic inhibition of the SNPr upon the SC (figure 4) and a consequent susceptibility to making uncalled for reflexive saccades. Other possibilities, though, should also be considered. A loss of tonic or of phasic inhibition by the frontal lobes, either directly upon the SC or indirectly via the CN, might also contribute to increased distractibility. Lesions in the cerebral hemispheres can lead to excessive errors on the antisaccade task. The dorsolateral prefrontal cortex may be the crucial region as it projects directly to the SC, and possibly indirectly, through the CN.
Effects of persistence or early removal of the fixation target on reflexive saccade latency—gap/overlap paradigms. Our patients with HD and the normal subjects showed the same effects on saccade latency of a change in the timing between the offset of the fixation target and the onset of the peripheral target. This result suggests that HD patients can disengage visual attention when a fixation target is removed in a normal fashion. Abnormalities in disengagement of visual attention have been reported in patients with parietal lobe lesions. It may be that gap-overlap effects on saccade latency are mediated by parietal structures; these areas are likely relatively spared in HD.

Prediction abnormality in HD. As expected, the HD patients showed a number of abnormalities in the predictive saccadic tracking task. Interestingly, in the HD patients, predictive tracking was improved when a non-localizing sound was also presented at the time of target displacement (paradigm PB), and predictive tracking was improved even more when only the sound was used as the cue for timing, though in the presence of continuously illuminated visual targets (paradigm PS). Our normal subjects also showed more anticipation of target motion in paradigm PS, but there was no significant difference when an auditory cue was simply added to the alternating lights (PL versus PB). The explanation for the increase in anticipation in the PS paradigm in normal subjects may be related to the specific instructions. In paradigms PL and PB the subjects were required to move their eyes in time with the light. Hence, if they anticipated by too much, their eyes would arrive—incorrectly—before the target was illuminated. In fact, the mean values for saccade latency in the PL and PB paradigms were such that the eyes arrived at the LED just as it would be turning on. On the other hand, in paradigm PS, since both LEDs were always illuminated, there was no “penalty” for arriving early, and the mean latency probably reflected the primary effect of the timing information abstracted from the auditory cue.

HD patients, however, showed better prediction in the PB paradigm and even better prediction in the PS paradigm. Presumably the auditory cue provided helpful timing information in the PB paradigm, while in the PS paradigm the continuous presence of the visual targets facilitated even further the ability to generate anticipatory saccades. This interpretation is compatible with the idea that HD patients have difficulty in making voluntary saccades to the remembered or learned locations of previously seen targets. Finally, for both HD and normal groups the degree of relative improvement in predictive tracking with auditory cues was not statistically significantly different.

Thus, the defect in predictive tracking in HD may be a relative inability to use spatially specific information (eg, target lights) to abstract both timing and location information for anticipatory behavior, while non-spatially specific cues (eg, nonlocalizable sounds) can be used relatively normally to augment anticipatory behavior. Furthermore, the deficits in generating predictive eye movements in HD may be a special example of a more generalized defect in generating voluntary eye movements in the context of remembered or learned behavior. The abnormality likely reflects involvement of excitatory pathways from the frontal lobes, either to the basal ganglia or directly to the SC, or reflects direct involvement of the basal ganglia itself (figure 4).

Patients with Parkinson’s disease (PD), in whom the CN may be malfunctioning due to a disturbance of the dopaminergic input from the substantia nigra, also show impaired predictive tracking. Involvement of the CN, which occurs in both PD and HD, may be responsible for the impaired predictive tracking capability that occurs in both conditions. Nevertheless, both monkeys and patients with structural lesions located in the frontal lobes also show defects in predictive saccadic tracking. Even patients with parietal lobe lesions may have impaired predictive tracking. Thus, a specific localization for deficits in predictive tracking must await further study in patients with lesions in different locations. Furthermore, the use of auditory and visual cues in predictive tracking tasks, with different combinations of timing and location information, may become useful in neurologic localization.

In sum, we have demonstrated several new features of the disorder of saccades in HD patients. The defects in predictive tracking are compatible with previous suggestions about the function of the frontal lobes and the basal ganglia in the control of saccades. Our results also suggest that characterization of predictive tracking and of the effects of gap and overlap paradigms on saccadic initiation time may be useful in the evaluation of saccades in patients with neurologic diseases.

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