Hypometric primary saccades and increased variability in visually-guided saccades in Huntington’s disease

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Received 18 March 2002; received in revised form 2 October 2002; accepted 18 March 2003

Abstract

Eye movement abnormalities can be distinctive and suggestive of a specific pathophysiology. To further investigate the deficits in the control of saccades in patients with Huntington’s disease (HD), we investigated the ability of 11 HD patients and 11 matched controls to perform visually-guided saccades. We adopted reflexive saccade tasks involving predictable and unpredictable sequences, at different amplitudes of target step (10°, 20°, 30°, 40°), as well as voluntary self-paced saccades. Prolongation of initiation was observed in the HD group as the target amplitude of predictable saccades increased. During the self-paced saccade task, the HD patients had increased intersaccadic intervals, performed fewer saccades in the allocated time and displayed an increased temporal variability in comparison to the controls. Furthermore, hypometric primary saccades, and an increased number of corrective saccades, were observed during both reflexive and voluntary saccades in the HD group. The delayed initiation of large saccades, deficits in voluntary, self-paced saccades, impaired saccadic accuracy and increased corrective saccades in HD, were interpreted in light of other ocular motor and limb studies, and appear to be due to damage to the fronto-striatal loop, including the supplementary eye fields, as well as possible brainstem and cerebellar involvement.

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Keywords: Basal-ganglia; Eye movements; Ocular motor; Voluntary saccades

1. Introduction

Huntington’s disease (HD) has traditionally been considered a disorder of the basal-ganglia (BG), with the neuropathological hallmark being progressive atrophy of the striatum (Harper, 1996; Vonsattel & DiFiglia, 1998; Vonsattel et al., 1985). More recently, evidence has highlighted the possibility of pathological changes occurring within the cortex (Aylward et al., 1998; Halliday et al., 1998), particularly frontal regions (Sotrel et al., 1991). The significance of degeneration within parietal regions (Bartenstein et al., 1997; Weeks et al., 1997), the cerebellum (Vonsattel & DiFiglia, 1998) and the brainstem (Koeppen, 1989) is less certain.

Saccades are rapid eye movements that bring images of interest onto the central region of the retina (Leigh & Zee, 1999). There are various types of visually-guided saccades. Reflexive saccades are generated in response to external and novel visual stimuli. Alternately, volitional saccades are internally generated to either existing visual stimuli or a remembered location of a previously visible stimulus. Volitional saccades may be further classified according to the behavioural context in which they occur. For instance, they may be generated to persisting visual targets, or anticipated in instances where the visual targets form a predictable sequence. Two parallel systems have been proposed to differentially govern reflexive and volitional saccades (Pierrot-Deseilligny, Rivaud, Gaymard, Muri, & Vermer, 1995).

Reflexive saccades are thought to be triggered by the posterior parietal cortex and the parietal eye fields, which have direct connections with the superior colliculus (SC) (see Chafee & Goldman-Rakic, 1988, 2000). The SC is the final region through which saccadic commands are relayed to brainstem structures that generate saccades. In contrast, volitional saccades are probably triggered from
frontal structures including the frontal eye fields and dorsolateral prefrontal cortex. From here, projections are also sent to the SC, either directly or via the BG (Leigh & Zee, 1999). This simplified model of two separate pathways suggests that selective lesions will differentially impair the two types of saccade. Likewise, abnormalities in saccades will reflect specific neural disturbances, thus providing the basis for inferring neuropathological changes in HD.

There is controversy as to whether saccadic abnormalities observed in HD are a consequence of dysfunction of the BG, brainstem or cerebellum (Bollen et al., 1986; Lasker & Zee, 1997; Lasker, Zee, Hain, Folstein, & Singer, 1987, 1988; Leigh, Parhad, Clark, Buettner-Ennever, & Folstein, 1985). Despite limited research, early and consistent ocular motor findings in patients with HD indicate difficulties in initiating voluntary, but not reflexive saccades, deficits in maintenance of fixation, and general saccade slowing (Avanzini, Gironti, Caracan, & Spreadsico, 1979; Lasker & Zee, 1997; Leigh, Newman, Folstein, Lasker, & Jensen, 1983). It has been reported that while saccadic slowing is frequently attributed to brainstem dysfunction, the initiation deficits in HD suggest disturbances to the fronto-striatal SC pathway, with sparing of the parietal SC pathway (Lasker et al., 1988; Leigh et al., 1985).

The accuracy of saccades in HD is unclear. Whilst it has been reported that HD patients display no impairments in the accuracy of reflexive or volitional saccades (Lasker et al., 1988, an earlier study reported hypometria (undershooting accuracy of reflexive or volitional saccades in HD (Bollen et al., 1986); however, these conclusions were based on descriptive information without statistical analyses.

The purpose of this study was to adopt the use of more accurate eye movement recordings, using the search coil method (Shaunak, O’Sullivan, & Kennard, 1995), to accurately define deficits in the initiation and accuracy of voluntary and reflexive saccades in patients with HD, in comparison to a control group. The ability of the HD group to perform eye movements in a consistent manner was also examined, with a general aim of providing further insight into the neuropathology of HD.

2. Methods

2.1. Subjects

Eleven patients with HD (mean age = 51.3 years, age range = 30–66 years) and 11 sex and age-matched normal, healthy controls (mean age = 51.3 years, age range = 32–63 years) with no history of neurological disorder, participated. All patients showed generalised choroises and have had genetic status confirmed. Disease duration ranged from 1 to 14 years. Severity of patient symptoms was assessed by a neurologist using the motor sub-scale of the Unified Huntington’s Disease Rating Scale (UHDRS) (Huntington Study Group, 1996); patients were scored between 19 and 62 (mean = 37.5, S.D. = 13.6), with higher scores indicative of increased severity. Clinical data for the HD group are shown in Table 1.

All participants had normal or corrected vision; spectacles could be worn in addition to the contact lens used for measuring eye movements. Information regarding age of disease onset, family history of HD, symptoms and current medication was also ascertained, see Table 1. The Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) was administered to screen for dementia, with all patients scoring above 20 (a score below 20 is indicative of dementia). No further cognitive evaluation was performed due to the relative simplicity of the ocular motor tasks. The Montgomery and Asberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979) was also administered. All patients were within the normal range, see Table 1.

All participants gave informed consent and ethics approval was given according to the NH&MRC criteria.

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Note: Mothers indicate the participant was not taking neuroleptic or depression medication. MMSE: Mini-Mental State Examination (maximum score: 30; a score below 20 is indicative of dementia). MADRS: Montgomery and Asberg Depression Rating Scale (0–19, no or minimal depressive symptoms; 20–30, exhibits depressive symptoms). UHDRS: Unified Huntington’s Disease Rating Scale (just items 6–12 and 14–20, i.e. those assessing motor function).
2.2. Eye movement recordings

Eye movements were measured using the magnetic field scleral search coil technique, using an EM3 Eye Movement Monitor (Remmel Labs) (Robinson, 1963), with a 320 Hz low pass filter. Participants were seated 114 cm in front of an arc (radius, 114 cm), which contained an array of nine light-emitting diodes (LEDs). LEDs were fixed at a central location of 0° and 5°, 10°, 15° and 20° in left and right horizontal directions. Head movements were restricted by the use of a head-rest, as well as manual restriction by the investigator. Head movement was monitored by the use of a head position coil, mounted on the forehead. Participants were in complete darkness, except for the LEDs.

A scleral coil was inserted into the participants’ dominant eye, after applying a topical local anaesthetic. Participants were positioned within the magnetic fields permitting the induction of current in the scleral coil, thereby enabling recording of eye movement (Robinson, 1963; Shaunak et al., 1995). The coil was pre-calibrated on a protractor device.

2.3. Procedure

Before the coil was inserted, and the commencement of data collection, participants were given instructions pertaining to each of the three protocols. They were to follow the lights in each protocol, given frequent reminders throughout the experiment and constantly alerted. Individual protocols were deliberately kept short to help maintain alertness. The protocols were ordered by increasing difficulty. It is unlikely there were any effects of fatigue or practice as the duration of the entire experiment was only 15 min.

In the predictable saccade protocol the LEDs were illuminated in a predictable (in regard to both spatial and temporal parameters) left-right, centre-crossing, sequence (i.e. −10°, 0°, +10°, 0°, −10°, . . .). There were four amplitude variations of this protocol: 10°, 20°, 30°, 40° steps (all ranging between +20° and −20°; where negative sign indicates to the left of straight ahead (0°) and positive indicates to the right). In all variations, each LED was illuminated for 2 s, in sequence and as one LED extinguished, the next LED immediately illuminated. The duration of each of these protocols was 2 min. During the 10° variation approximately 30 saccades were elicited and, on average, 25 saccades were elicited during the protocols with larger amplitude steps. Participants’ ability to make reflexive saccades to stimuli appearing in a predictable fashion was therefore examined, as well as the effects of increasing target amplitude.

In the unpredictable saccade protocol, LEDs were illuminated in a horizontal, yet random direction (right or left), with pseudorandom amplitudes between 5° and 40°, resulting in an overall equal number of saccades made at each amplitude. Each LED was illuminated for 2–6 s in a pseudorandom order, and as one LED extinguished, the next LED immediately illuminated. The protocol duration was 2.5 min, with approximately 40 saccades elicited. Participants’ ability to make reflexive saccades to unpredictable stimuli was examined.

In the self-paced protocol there were two LEDs, set 20° apart (i.e. −10° and +10°) that were both continuously illuminated for the duration of this protocol ~1.5 min. Participants were additionally instructed to “alternate your eyes between the lights” and to “try to get to the target as quickly and accurately as possible.” Participants’ ability to initiate voluntary saccades to continuous stimuli and to disengage from continuous stimuli was therefore examined.

2.4. Data analysis

The output of the magnetic scleral search coil technique was acquired on a Pentium II, 200 MHz computer using a Digidata 1200 12-bit Acquisition board and Axolab software. The sampling rate of data acquisition was 1 kHz. Data were subsequently analysed offline, using an interactive computer program. Since the self-paced task was conducted at an amplitude of 20°, all analyses involving the self-paced task also used saccades of a 20° amplitude. Within the unpredictable protocol, nine saccades with an amplitude of 20° were extracted and analysed. For comparison purposes, all analyses involving the unpredictable protocol also used nine saccades, which were extracted from the middle range of saccades made within each protocol. It should be noted that we did not differentiate between centripetal and centrifugal saccades and we had an approximately equal number of centripetal versus centrifugal saccades.5

The temporal measures considered were peak velocity of saccades, determined by computer differentiation of the position trace. Saccade latency, defined as the time between target onset and the commencement of the primary saccade, was used in reflexive protocols. Alternately, the intersaccadic interval was the time between the end of one saccade and the commencement of the next saccade in the self-paced task. A position trace was used to determine when a saccade occurred and the basis of a saccade was determined by the departure from the baseline. The beginning and end of a saccade were determined visually, according to changes in the velocity profile of the saccadic trace (see Fig. 1). Correction time represented the time taken from the end of the primary saccade, while corrective saccades were made, until the final eye position was reached. To investigate the consistency of each participant’s eye movements, the variability of temporal measures, in terms of standard deviation of the intersaccadic intervals and the correction time was also addressed for the self-paced protocol. Temporal measures were averaged across individual saccades for each protocol.

5 It is of note that only horizontal components of saccades were examined for these protocols. Although vertical eye movements were recorded for other protocols that examine oblique eye movements (in preparation), the data was not examined or retained for the purely horizontal protocols included in this publication.
Fig. 1. An example of a horizontal saccade made 20° to the right in a control participant. For saccadic analyses, four cursors were placed: (A) at target onset, (B) at the beginning of the primary saccade (when the velocity changes), (C) at the end of the primary saccade (when the velocity of the initial horizontal saccade line changes) and (D) at the final eye position (reached when the horizontal saccade line remains constant). The increased number of corrective saccades (indicated by (∗)) can be seen in the Huntington’s disease patient compared to a control participant (CON).

Three accuracy measures compared the reflexive (unpredictable) and voluntary (self-paced) tasks. Percentage gain represents the amplitude achieved in the primary saccade compared to the final eye position (i.e. the degree of dysmetria of the primary saccade), expressed as a percentage. An average was calculated across saccades for each individual in the self-paced and unpredictable protocols. The mean and standard deviation of the saccade error (i.e. the error from the desired amplitude of 20°) was considered for both the primary saccade and the final eye position.

The number of corrective saccades, the number of self-paced saccades and the percentage of anticipatory saccades (all saccades within the 10° predictable protocol occurring prior to target onset, or within 0.12 s were considered anticipatory (Leigh & Zee, 1999)), were also derived for each participant.

In cases where a Levene’s test for equality of variance indicated no significant difference between the variance of the two populations ($P > 0.05$), statistical comparisons were based on ANOVAs and Student’s $t$-tests. Alternatively, in cases where the Levene’s test was significant, $t$-test results for unequal variances were adopted.

3. Results

3.1. Anticipatory saccades

During the predictable saccade protocol, the control group made a greater percentage of anticipatory saccades (mean = 20.0% anticipatory saccades) in comparison to the HD group (mean = 8.93% anticipatory saccades), $F(1, 20) = 4.18$, $P = 0.05$.

3.2. Temporal measures

3.2.1. Reflexive saccades

HD patients showed a trend toward decreased peak velocities for 20° reflexive saccades (mean = 291.91°/s, S.D. = 129.17) in comparison to the control group (mean = 2
As the target amplitude increased in the predictable protocol, saccadic latencies in the HD group increased significantly, in comparison to the control group (Fig. 2). There was no significant difference between the saccade latencies for the reflexive saccades (mean = \( 20.29 \) s) compared to the control group (mean = \( 20.18 \) s). In addition, the HD group had significantly greater variability in the correction time period (mean = \( 20.50 \) s) in comparison to the control group (mean = \( 20.32 \) s). Post-hoc one-way ANOVAs revealed the HD group had significantly greater variability in the intersaccadic interval (mean = \( 20.45 \) s) compared to the control group (mean = \( 20.37 \) s). A significant interaction was also found between group and temporal parameters, \( F(2, 40) = 3.43, P < 0.05 \). Regardless of protocol, the HD group had an increased correction time (mean = \( 0.51 \) s) in comparison to the control group (mean = \( 0.35 \) s), \( F(1, 20) = 5.25, P < 0.05 \).

In addition, during the correction time period, in both the reflexive (unpredictable) and self-paced (voluntary) protocols, the HD group made significantly more corrective saccades (mean = \( 1.58 \) corrective saccades), than the control group (mean = \( 0.98 \) corrective saccades), \( F(1, 18) = 16.74, P < 0.001 \) (refer Fig. 1 for an example of a corrective saccade).

3.2.2. Voluntary saccades

The intersaccadic interval during the self-paced saccades (mean = \( 0.70 \) s) was significantly greater than the saccade latencies for the reflexive saccades (mean = \( 0.25 \) s) in both groups \( F(1, 20) = 20.07, P < 0.001 \). The difference was somewhat greater (although there was no significant interaction) for the HD group. However, during the self-paced saccade task, the HD group made significantly less self-paced saccades in the allocated time (mean = \( 40.64 \) saccades) compared to the control group (mean = \( 72.64 \) saccades), \( F(1, 20) = 10.73, P < 0.01 \).

3.3. Temporal variability

The HD group displayed large amounts of variability during their performance in the self-paced task, see Fig. 3. A two-way ANOVA indicated a significant main effect of group \( F(1, 20) = 11.07, P < 0.01 \) and a significant main effect of temporal parameters, \( F(2, 40) = 34.087, P < 0.001 \). A significant interaction was also found between group and temporal parameters, \( F(2, 40) = 3.43, P < 0.05 \).

Post-hoc one-way ANOVAs revealed the HD group had significantly greater variability in the intersaccadic interval (mean = \( 0.56 \) S.D.) compared to the control group (mean = \( 0.28 \) S.D.), \( F(1, 20) = 6.90, P < 0.05 \). In addition, the HD group had significantly greater variability in the correction time period (mean = \( 0.35 \) S.D.) compared to the control group (mean = \( 0.19 \) S.D.), \( F(1, 20) = 6.13, P < 0.05 \). Furthermore, a Pearson’s correlation revealed that the scores on the motor sub-scale of the UHDRS were positively correlated with the variability in the correction time during the self-paced task.
Fig. 3. Temporal variability: the amount of temporal variability in the individual performance of self-paced saccades in the HD and control (CON) groups (where zero equals no variation) across the latency, intersaccadic interval and correction time parameters. (*) Denotes statistical significance (P < 0.05).

Of all the dependent variables, this was the only significant correlation.

3.4. Accuracy

Patients with HD showed hypometric primary saccades compared with the control group, with both groups showing accurate final eye positions. Results of a two-way ANOVA indicated a significant main effect of Group, $F(1, 20) = 8.29, P < 0.01$; patients with HD showed hypometric primary saccades (mean = 84.44% of the final eye position achieved in their primary saccade) compared to the control group (mean = 93.05% of the final eye position achieved in their primary saccade). A significant main effect for Saccade Type was also revealed, $F(1, 20) = 14.97, P < 0.001$. The percentage gain was greater in the voluntary (mean = 92.14%) compared to the reflexive (mean = 85.34%) tasks. No significant interactions were found between group and saccade type $F(1, 20) = 0.16, P > 0.05$.

3.4.1. Variability in accuracy

In regard to the mean saccadic error, which reflects the average error a participant makes with regard to the target amplitude, the results of a two-way ANOVA indicated that both the HD and control groups were undershooting the target amplitude. As expected there was a significant improvement in accuracy between eye position at the end of the primary saccade (mean = −4.06°) and the final eye position (mean = −2.08°), $F(1, 20) = 66.77, P < 0.001$. This effect was greater in the HD group, with a significant interaction being found between group and eye position $F(1, 20) = 9.85, P < 0.05$.

As seen in Fig. 4, the accuracy of the saccades for the HD individuals was significantly more variable than that of control individuals in both protocols and for both eye positions. Results from a three-way ANOVA indicated a significant main effect of Group $F(1, 20) = 11.43, P < 0.01$. The HD group had a greater amount of error variability (mean = 2.21 S.D.) than the control group (mean = 1.07 S.D.).

4. Discussion

The major and novel findings of this study were, in HD patients:

- impaired initiation of saccades with larger target amplitudes,
hypometric primary saccades followed by an increased number of corrective saccades,

- significantly increased variability in saccade performance, both in terms of accuracy and temporal parameters.

Confirming previous findings, HD patients displayed impairments in anticipatory saccades (Tian, Zee, Lasker, & Folstein, 1991), and those with earlier onset HD possibly displayed slower saccades (Lasker et al., 1988). A trend was also observed for impaired initiation during voluntary, self-paced saccades amongst the HD group. It is unlikely that medication impacted upon these results, as only two of our patients were taking haloperidol and only one patient was taking tetrabenazine (sertraline and fluoxetine are antidepressants). Moreover, on inspection of individual data, the same pattern of abnormalities was noted between patients who were and were not taking medication.

Unlike controls, HD patients experienced difficulties initiating predictable, reflexive saccades when the target amplitude increased beyond 20°, to amplitudes of 30° and 40°. Head movements, that would normally accompany these larger saccades (Stahl, 2001), were restricted in this study. Since this task required participants to perform relatively novel, or unrehearsed, eye movements (large saccades in the absence of head movements), this finding suggests that learning of new ocular motor programs may be impaired in HD, a finding previously reported in upper-limb studies (Georgiou, Bradshaw, Phillips, Chiu, & Bradshaw, 1995; Heindel, Butters, & Salmon, 1988). The frontal-striatal circuits, which are thought to be compromised in HD (Thompson et al., 1988; Vonsattel, 1999), are believed to mediate the learning of new motor programs (Tomlinson & Bahra, 1986).

HD patients made significantly fewer self-paced saccades than controls, and showed significantly increased variability in the timing of their self-paced saccades. In addition to the regions involved in voluntary saccades, repetitive, self-paced saccades are controlled by the supplementary eye fields, a region of the supplementary motor area (SMA) and the cerebellum (Pettit et al., 1993). The degree of neuropathological damage to the cerebellum in HD remains unclear (Vonsattel, 1999). Therefore, one can only speculate what role cerebellar dysfunction may play in self-paced deficits. It is, however, well accepted that the SMA may be compromised in HD, via dysfunction of the cortico-striatal loop (Cummings, 1993).

Temporal abnormalities are seen in other movements in HD. Stride-to-stride variability of gait timing is significantly increased in HD patients, compared to controls (Churchyard et al., 2001; Hausdorff, Cudkowicz, Firtion, Wei, & Goldberger, 1998; Phillips et al., 1996). It has been suggested that the gait variability reflects faulty motor programming, mediated by the BG and its SMA connections. The variability observed in gait studies increases significantly with HD severity (Hausdorff et al., 1998), a finding also observed in this study; increased variability during the correction time phase of the self-paced task correlated significantly with increased disease severity in HD participants (indicated by increased scores on the motor sub-scale of the UHDRS). It is likely that the supplementary eye fields, during the self-paced saccades, play an analogous role to the SMA in self-paced movements. That is, the BG are involved in timing cued events, triggering a build-up of activity in the SMA (Cunnington, Iansek, Bradshaw, & Phillips, 1995), or in this case, possibly the supplementary eye fields.

In conflict with some previous literature (Lasker et al., 1988), HD patients in this study displayed hypometric primary saccades, followed by an increased number of corrective saccades, which did not correlate with disease severity. Parkinson’s disease patients, whose pathophysiological
Visual feedback (via cortical regions) was used to trigger HD patients, corrective saccades were generated, until an tendency until the desired eye position is reached (Leigh & Zee, 1999). Indeed, after the hypometric primary saccade in the particular direction and amplitude. Local brainstem feedback mechanisms may then continuously compare the desired eye position with the actual eye position (efference copy), thereby generating further corrective saccades at a short latency until the desired eye position is reached (Leigh & Zee, 1999). Indeed, after the hypometric primary saccade in the HD patients, corrective saccades were generated, until an accurate final eye position was achieved. It is unlikely that visual feedback (via cortical regions) was used to trigger corrective saccades as, on a descriptive level (see Fig. 1), it appears that corrective saccades were generated at latencies less than 120 ms, the time required for cortical input (Leigh & Zee, 1999). Thus, it is possible that the appropriate message regarding desired eye position was relayed to the brainstem. Within this region omnipause cells discharge continually, inhibiting burst cells, except immediately prior to, and during saccades, when they pause and permit burst cells to fire, thus enabling a saccade to be performed. If omnipause cells are dysfunctional, or stimulated during a saccade, the saccade is aborted mid-flight, creating a dysmetric initial saccade (Keller & Edelman, 1994). Furthermore, lesions within the omnipause region, or the excitatory burst cells they project to, lead to saccadic slowing (Kaneko, 1996), a common explanation for the slow saccades evident in HD (Lasker & Zee, 1997; Lasker et al., 1988). Despite limited evidence, atrophy and increased neuronal densities have been noted in the omnipause region in HD patients (Koeppen, 1999); this may account for some of the current deficits observed in HD. A third explanation for the hypometric primary saccade (in addition to the saccade slowing) may invoke dysfunction in the regions that project to, and co-ordinate, omnipause function, as suggested by Lasker and Zee (1997). Omnipause cells receive projections from the rostral pole of the SC, the frontal and supplementary eye fields, midbrain and cerebellar regions. Indeed, the frontal and supplementary eye fields, of the frontal lobe, are considered to be compromised in HD (Bartenstein et al., 1997; Halliday et al., 1998). This study, for the first time, has demonstrated that HD patients have increased variability in the timing of self-paced saccades and display hypometricity of voluntary and reflexive primary saccades, followed by an increased number of corrective saccades, that did not correlate with disease severity. We believe that the deficits observed in HD are not explained fully on the basis of cortical or BG disease, but may be explained by the combination of pathology in these regions, perhaps in conjunction with cerebellar dysfunction and primary brainstem disease.

Acknowledgements

The authors would like to thank Eli Lilly Pty Ltd. for their generous support of the laboratory and Roman Capel for his assistance with configuration of the laboratory. The authors would also like to thank all the HD patients and controls who participated in this study for their time and patience.

References


