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Longitudinal saccadic changes in Huntington's disease and Alzheimer's disease◇#

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ABSTRACT. Saccadic latency and velocity-amplitude relationships were examined over approximately six years in two patients, one with Huntington's disease (HD) and one with Alzheimer's disease (AD). In both cases this was a period that began relatively early in the course of the disorder and included significant clinical deterioration. The HD patient showed markedly slow saccades upon initial recording; subsequent studies showed some velocity fluctuations without a clear trend. Latency varied similarly, generally being close to normal.

In contrast to the HD patient, the AD patient's first two studies showed *normal* saccadic latencies and velocities. Also, the latency suddenly became significantly prolonged one year prior to the time that her dementia progressed.

Both patients showed a significant correlation, from session to session, between latency and peak velocity asymptote; this, despite the marked differences in the way their diseases affected these saccadic characteristics. Longer latencies corresponded to lower peak velocities, suggesting a common source, arising in the frontal eye fields, for difficulties in both saccadic initiation and motor programming.

Key words: Huntington's disease; Alzheimer's disease; saccades; latency; velocity

INTRODUCTION

Two of the numerous neurological disorders affecting ocular motility are Huntington's disease (HD) and Alzheimer's dementia (AD). The former disorder has been associated with slow saccades, increased saccadic latency, hypometria, defective saccadic suppression and impaired pursuit[1-5]. Alzheimer's patients have been less frequently studied in this context, but abnormalities include increased saccadic latency, hypometria, defective saccadic suppression and reduced pursuit gain (as indicated by an increase in the number of catch-up saccades)[6-9]. Marked saccadic slowing has been observed in HD but not in AD patients. Hutton[10] described a deteri-

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oration over time in the smooth pursuit of AD patients.

At the time of the initiation of this study, no publications provided information about possible changes in saccadic defects over time or their correlation with the clinical course of these diseases in any particular patient. During the course of this study, several others have appeared in addition to those cited above. One[11], using EOG, found that average saccadic velocity was slowed in 75% of HD patients and concluded that it was a good diagnostic sign in patients at risk for HD. Although they did record six subjects 'at risk' and four HD patients with normal velocities, on two occasions, the bulk of the HD patients were recorded only once. Others[12, 13] have found slow saccades or long saccadic latencies in some HD patients. The variability of deficits found in saccadic characteristics for both these patient populations precludes their universal application for diagnosis or prognosis of severity of the diseases. However, there remains the possibility, not evident in data taken from large numbers of patients at different times in their variable courses of disease, that for any given patient a change in one or more of these characteristics could precede other clinical signs of deterioration. If so, early recordings could provide the necessary baselines with which later data could be compared. It is with this in mind, that we undertook the systematic, longitudinal study of both an HD and an AD patient. We were able to follow both patients oculographically and clinically for six years beginning early in the course of their illnesses, and have documented differences in how the eye movement abnormalities in these two dementing disorders have changed.

PATIENT HISTORIES

The first patient was admitted in August, 1980 to the Cleveland Veterans Administration Medical Center at age 44 with a diagnosis of Huntington's disease. Histories of her father, uncle and grandfather were all consistent with this diagnosis (both patients were diagnosed by members of the Department of Neurology, Case Western Reserve University). Her initial signs were an occasional slurring of speech, hyperreflexia, rare adventitious movements, and a slightly dystonic gait. Her family reported that she was 'forgetful and clumsy.' Psychological evaluation in December, 1980 revealed moderate memory impairment with particular problems in attention and concentration, although her Verbal I.Q. remained in the average range. Scores on performance tasks were considerably poorer. The most striking deficits were in tasks requiring visual scanning, manual manipulation of stimulus materials, and speed.

Her course since that time has been marked by increasingly dysarthric speech and development of an ataxic gait, although there was minimal clinical progression of the disease thrgh 1983. Athetoid movements of the tongue and slow saccades were noted clinically in 1982, spasticity in 1983. Choreiform movements while walking and subtle adventitious movements at rest were noted in 1984. The patient continued to live at home with her mother and serve as a hospital volunteer through most of 1987. Psychological evaluation in 1987 revealed that, although many aspects of cognitive functioning have remained quite stable, there has been progressive deterioration in areas of impairment noted on initial testing. The patient was highly distractable, motorically slower and had her performance further impaired by involuntary movements.

The other patient, first seen in October, 1981, was a 68-year-old woman who presented with a history of progressive intellectual change over a two- to three-year period. Upon her initial examination she was unable to give the day of the week or date. She was unable to give either her own or her daughter's address. She had difficulty in identifying the recent presidents. Complex constructions, reading and writing, object identification, comprehension and spontaneous speech were all normal. She was living independently at the time having no problems with her basic, and limited problems with instrumental, activities of daily living. A presumptive diagnosis of Alzheimer's disease was made. Her next assess-

ment was in August, 1985. Episodes of mild confusion were reported. Some deterioration in cleanliness had occurred. There was difficulty in following complex instructions. She continued to live independently, with frequent visits by a companion. Her neurologist's clinical impression was that she was maintaining a level of functional effectiveness. Over the following year, the companion and daughter noted increasing forgetfulness and the appearance of delusions that unknown individuals were taking her mail and coming into her house and stealing things. The frequency of companion visits was increased to once a day, as her ability to function independently became more marginal. Her most recent assessment, in June, 1987, found her to have lost a significant amount of weight due to her forgetting to eat. Her personal appearance and hygiene had also deteriorated. Her short-term memory loss has become more severe, as did her belief that people were coming into her house and stealing things. The recommendation was made that an intermediate care facility be considered, as she could no longer safely live in her own home, even with daily visits from a home aide.

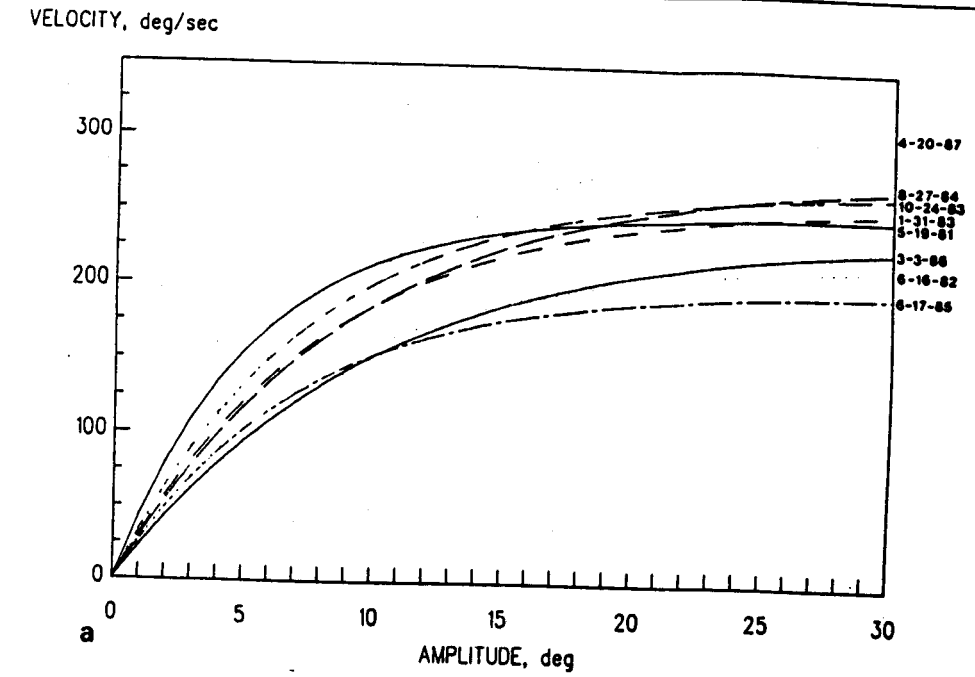
METHODS

We carried out a computer-based evaluation of saccadic latency and velocity-amplitude relationship in both patients. The HD patient was recorded eight times over the last six years; the AD patient was recorded five times over a 5½ year period. Stimuli were red light-emitting diodes turned on and off in a pseudo-random sequence approximately every two seconds by a Digital Equipment Corporation MINC-11/23 microcomputer; target jumps went between 0° and targets ranging from ±2 to ±20°, as well as between +15 and −15°, so that approximately 80 saccades from 2 to 30° were evaluated at each session. Subjects were instructed to look at the lights and follow them when they jumped to a new position; repeated encouragement was given during the course of all sessions. We did not attempt to bias their attempts towards either speed or accuracy but just instructed them to follow the lights as best they could. Eye movements were recorded using DC infrared oculography; signals were filtered at 100 Hz and digitized by the computer at 200 samples/sec. They were also displayed on a Beckman R612 Dynograph. Data were analyzed off-line for position, velocity and latency. We described the saccadic velocity-amplitude relationship for each session in the same manner as has been used by most researchers in this field for the past two decades. That is, best mean-square fit curves of the form $V=V_{max}(1 - e^{-A/K})$ were fit to the resulting velocity-amplitude plots, where V = peak saccadic velocity, V_{max} = velocity asymptote, A = saccade amplitude and K = the amplitude equivalent of a time constant (details of the recording procedures, computer analyses and examples of the accuracy of fitted curves to the data may be found in Abel *et al.*[14]. Plots were made of these fitted curves (Figs. 1a and 1b) and of latency versus time since first recording (Fig. 2).

RESULTS

A striking finding in *both* patients was that neither showed a marked deterioration in saccadic velocities over the six years that they were followed. Even though the Huntington's disease patient deteriorated in several clinical measures, including motor function, no corresponding trend was observed in her peak saccadic velocities over the period of study. Indeed, her most recent test showed the highest value for V_{max}, the velocity asymptote (normal value from our laboratory for elderly subjects is 560). This recording and all others, however, did show subnormal peak velocities. Her saccadic latencies varied slightly throughout the testing period also, with no time-related trend being present.

The patient with Alzheimer's disease also



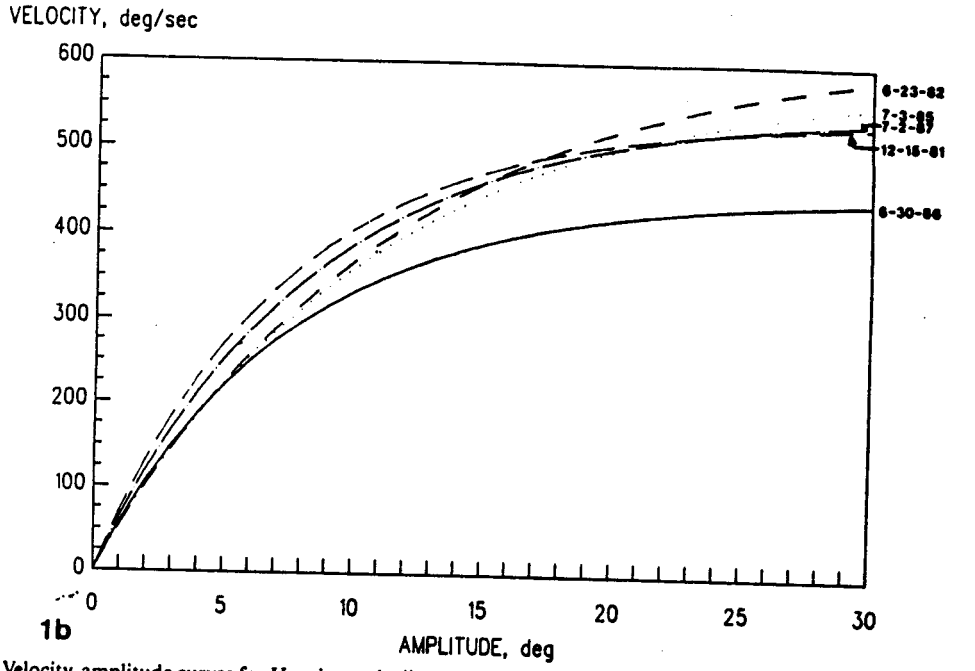


Fig. 1. a. Velocity-amplitude curves for Huntington's disease patient, shown with dates of recording. All are slower than normal for her age. No trend over time was observed. b. Velocity-amplitude curves for Alzheimer's disease patient. All were within normal limits and all were tightly clustered, except for the 6/86 recording.

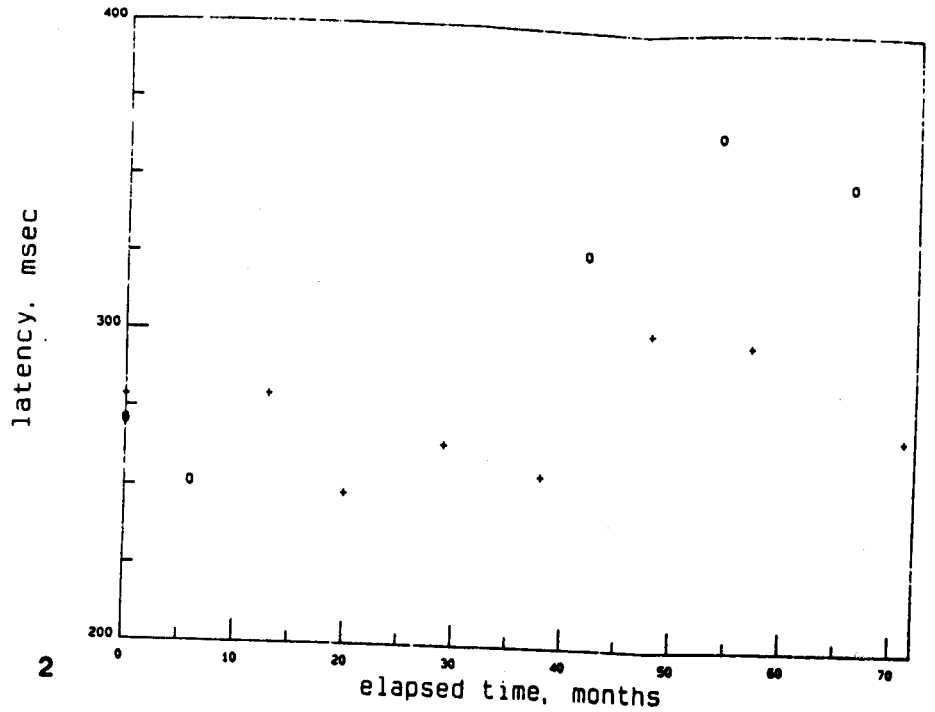


Fig. 2. Saccadic latency vs. elapsed time since first recording for the HD (+) and AD (o) patients. Standard deviations are not shown, but were large, ranging between 70 and 175 msec. For AD patient, first two values were significantly lower than last three (Student's t-test, $p < 0.01$), but no significant differences were found between the first two or any of the last three.

failed to show any trend towards slower saccades with time and disease progression. Her saccades remained within normal velocity limits throughout the course of the study. Only her fourth recording was slower than her others, but within normal limits for her age. However, a persistent increase was first seen in her saccadic latencies, beginning in 1985. This preceded by at least a year the marked intellectual decline that was subsequently observed by her companion, her family and her neurologist. Her latencies have moved from being *shorter* than those observed previously for elderly normal subjects[14] to being *significantly longer.* This change in latencies was sudden and apparently permanent.

Because both patients displayed considerable, albeit different types of variability in both their saccadic latencies (L) and peak velocity asymptotes (V_{max}), these two measures were plotted against one another in an effort to determine whether their velocity and latency fluctuations were independent or related. As can be seen in Fig. 3, a relationship appears to exist – faster saccades tended to have shorter latencies. For the HD patient, the equation of the regression line was $L = -0.338V_{max} + 360.1$, with a correlation coefficient $r = 0.652$ and for the AD patient, $L = -0.513V_{max} + 525.8$ with $r = 0.687$. For the AD patient, the large slope caused by the dramatic and persistent increase in latency after the second recording may not accurately reflect a single mechanism that affects both latency and peak ve-

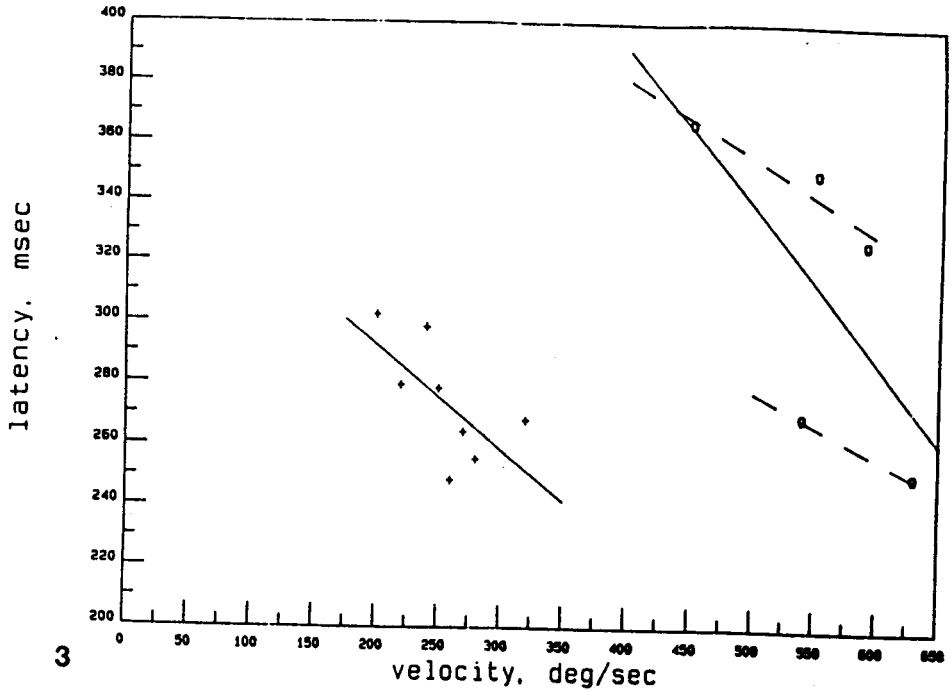


Fig. 3. Saccadic latencies vs. asymptotic velocities for each of the recording sessions for the HD (+) and AD (o) patients. Note that there appears to be an inverse relationship between latency and velocity. Regression lines are given in the text.

locity. Therefore, lines were fitted to each of the distinct data clusters separated by the permanent latency change. The equations of these regression lines were: $L = -0.211V_{max} + 384.0$ and $L = -0.256V_{max} + 483.0$ with $r = 0.940$ for the latter (only two recording sessions determined the first line).

DISCUSSION

The previously mentioned studies on both HD and AD have shown these disorders to have significant effects on ocular motility. Although these investigations have involved larger numbers of patients, each was examined only once. Alternatively, we chose to follow two patients (one with each disorder) and were able to obtain quantitative data for each of these different and difficult to record types of patients over approximately a six-year period. In both cases, the investigations began within one year after diagnosis, so that they were carried out during a time in which significant clinical deterioration occurred in both patients. The results of the saccadic testing showed striking differences in the two patients. The HD patient had *marked saccadic slowing* to unpredictable stimuli (and hypometria, not quantified in the present study) even at her first recording. Indeed, an early recording made with predictable stimuli was made in September, 1980, one month after her initial diagnosis; even then, her saccades were grossly slowed. In the following six years, despite the worsening of her clinical condition, her sac-

cades showed no consistent changes. This suggests that in Huntington's disease the saccadic system may be affected early and severely but with a stable level of dysfunction and is in contrast to the progressive nature of other neurological signs and symptoms. In general, she was able to initiate saccades with a relatively normal latency, but the resulting movements were extremely slow. Unlike the slow saccades seen in spinocerebellar degeneration,[15] however, no progression was observed. In four HD patients with normal saccadic velocities, it was found that only two showed abnormally slow velocities on retesting one to three years later and some with HD for over ten years still had normal velocities[11].

In contrast, our Alzheimer's patient showed *no saccadic defects* during the first and second recordings. At that time her symptoms were quite mild and she was able to live independently with minimal assistance. When recorded again (after a two-year gap) her saccadic latency had jumped significantly (Student's t-test $p < 0.05$). It was not until one year later that her clinical deterioration was severe enough to warrant an increase in the amount of assistance needed for daily living. Her latencies have remained at this elevated level since then, during which time the patient has deteriorated enough to require institutionalization. This correlation between increase in latency and in severity of dementia differs from our findings[7], and those of others[9], in a population of Alzheimer's and other dementia patients but is consistent with the report by Pirozzolo and Hansch[6]. Both of these were non-longitudinal studies of small populations. It may well be that only in some individuals are dementia severity and saccadic latency correlated; they were in our patient. After recording #4, it also appeared that a relationship might exist between dementia severity and velocity, since velocities were markedly lower. Their recovery to previous levels in recording #5, however, suggests that the decline was due to transient factors such as tiredness rather than to disease progression.

An additional and unexpected finding in the present study was the relationship between saccadic latency and peak velocity asymptote (none was found between latency and K, however). Both subjects showed, *on an intersession basis*, a correlation between increased latency and lowered peak velocity asymptote. Such a correlation has not previously been described in either patients or normals. Also, we think it significant that the two lines fitted to the data for the AD subject (pre- and post-latency increase) have virtually the same slopes. This suggests an underlying mechanism that affects both saccadic characteristics and that may be relatively insensitive to disease-induced changes in either. Since there was no relationship to K (a parameter more influenced by smaller saccades) and there was one to V_{max} (a parameter related to larger saccades), we hypothesize that latency is related to variations in burst duration rather than firing frequency. Variations in saccadic velocity have been observed both within[16, 17] and among subjects[14, 18-20]. Several of these studies have also observed different ranges of saccadic latencies. Group mean latencies were longer and velocities lower for elderly normals than young ones[14, 19, 20], but such averages do not imply a relationship between these variables. Reduction in saccadic velocity has been ascribed to fatigue, either in the sense of lowered vigilance or reduced neuromuscular function[16, 17, 21]. The latter work, in particular, considered the possibility of circadian variations in vigilance as being responsible for fluctuations in velocity. None of these investigations examined saccadic latency in relationship to velocity; this is not surprising, since saccadic initiation has generally been examined independently of those neural processes involved in the programming of the movement it-

self. Having previously noted the considerable impact that 'tiredness' can have on saccadic velocity, we feel that it may also play a role in increasing the time needed to begin a saccade. Sequential studies of normal individuals under differing conditions of alertness are necessary to determine whether this effect is present in unimpaired subjects and is an integral part of the saccadic control system. The presence of a velocity-latency relationship in two patients with different diseases suggests that this finding may reflect a more general relationship.

It would also be of interest to examine a large population of normal subjects to see whether those with consistently higher velocity saccades also had shorter latencies. Prompted by this study, we did find such a relationship for elderly but not young subjects[22]. It has been observed in monkeys that lesions of the frontal eye fields, a region important for saccadic initiation, cause slowing of memory-guided saccades, although visually-guided refixations remained normal[23]. The authors of that study pointed out that this implies that the frontal eye fields are involved not only in targeting and triggering saccades but also in programming their dynamic behavior. Both HD and AD patients show some defects of fixation, such as impersistence of gaze[4, 9] that have been associated with frontal eye field defects[24]. In addition, mild and marked slowing of saccades has been reported in patients with frontal lobe lesions and cerebral hemidecortication respectively[25]. If it is a subtle fluctuation in frontal dysfunction that is causing both the latency and velocity changes, then a similar relationship in normal individuals might exist.

In summary, the relationship we have found between the velocities and latencies of saccades in individuals is *not* equivalent to the effects of aging or intellectual decline[9]. If it exists in young normals, as it did in these two patients and in a population of elderly normals, models of the saccadic system will need revision.

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