Reliance on Advance Information and Movement Sequencing in Huntington’s Disease

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Summary: To identify the focus of impairment in the performance of sequential movements in Huntington’s disease (HD) patients, the extent of their reliance on external advance information was examined. Twelve patients with HD and their age-matched controls performed a series of button-presses at sequential choice points along a response board. A sequential pathway was designated, and with each successive button press, advance visual information was systematically reduced to various extents in advance of each move. HD patients, like previously studied parkinsonian patients, were particularly disadvantaged with high levels of reduction in advance information, and as a consequence, both their initiation and execution of movements progressively slowed with each successive element in the response sequence. The pattern of results was not affected whether or not patients were taking neuroleptic medication, nor did performance on a variety of cognitive measures correlate with motor performance. Control subjects’ performance, on the other hand, remained constant in terms of both initiation and execution with each of the three levels of reduction in advance information. We conclude that HD patients, like parkinsonian patients, who also suffer from a basal ganglia (BG) disorder, require external visual cues to sequence motor programs effectively. Our findings suggest that with HD there may be abnormalities in a central mechanism that controls switching between movement segments within an overall motor plan. The BG, which provide internal cues necessary for component sequencing, may be disrupted, thereby impairing the ability to use such internally generated cues to guide movement. Key Words: Huntington’s disease—Advance information—Internal cues—Basal ganglia.

Huntington’s disease (HD) is a progressive neurodegenerative disorder, generally characterized by the onset of uncontrollable choreiform movements, impaired voluntary movements, cognitive deterioration, and affective and psychiatric symptoms. It is inherited by autosomal dominant transmission and has complete lifetime penetrance (1).

The movement disorders and mental changes of HD are a consequence of progressive and selective neuronal degeneration within the basal ganglia (BG) and, to a lesser extent, in other brain areas. Dysfunction and death of cells within the BG is associated with increased concentrations of dopamine, serotonin, and norepinephrine, and a decrease of \( \gamma \)-aminobutyric acid and cholinergic synthesizing enzyme (2). Brain-imaging techniques, such as magnetic resonance imaging (MRI) and computerized tomography (CT), have typically revealed progressive bilateral atrophy of the striatum (caudate and putamen) in the early stages of the illness and more global cortical atrophy (beginning in the frontal lobes) in its later stages (3–6). Moreover, high-
Consequently, disturbances of motor coordination especially in the frontal and parietal regions (7), lentiform nuclei, as well as in the cerebral cortex, cerebral blood flow reductions in the caudate and putamen (8-10) are important and fundamental features, which may be prominent not only in the later course of the illness but also early in the disease, even when the predominant neurological sign is chorea (10). Whereas chorea may increase and then decrease as the disease progresses, akinesia/bradykinesia progressively worsens (11).

Prolonged movement times (MTs) have frequently been reported in patients suffering from both Parkinson's disease (PD) and HD. For example, HD patients have significantly slower MTs than controls when performing repetitive tapping movements (12). Significant slowing of MT has also been reported among HD patients and certain relatives at risk of the disorder during self-paced single isometric forefinger executions and alternating forefinger movements (13). Moreover, HD patients not only may show evidence of slow MT with simple wrist flexions but may also be significantly slower in combining two movements (i.e., hand squeezing and elbow flexing) in a sequential movement task (10). The bradykinesia evident in this last study was independent of whether or not the patients were taking neuroleptic medication. Girotti et al. (14) also reported that MTs were considerably slower in HD patients as compared with controls and with parkinsonian patients. Jahanshahi et al. (15) employed a simple reaction time (SRT) and a choice reaction time (CRT) paradigm and found that HD patients had significantly longer SRT than parkinsonian patients. PD patients were able to respond faster in the SRT task compared to an uncued CRT procedure, whereas for patients with HD, this SRT/CRT difference was not significant. Agostino et al. (16) studied the performance of sequential arm movements in HD, PD, and dystonic patients. All patient groups, especially HD patients, were considerably slowed in movement execution (i.e., MT), and in switching from one movement to the next. They also found that whereas PD patients showed a progressive slowing of MT as the sequence became more complex, patients with HD did not. We find these observations surprising in terms of the pervasive BG damage caused by the disorder; indeed, we previously found that HD causes problems both in utilizing and in incorporating advance information into sequential movement (17).

In a sequential button-pressing procedure, we reported (17) that HD patients have particular difficulty in executing movements at both low and very high levels of provision of advance information and in initiating movements at low levels of advance information. Very similar results were found using the same technique with parkinsonian patients (18). As with PD, HD patients seem to have difficulty in using advance information and in generating appropriate motor programs. The impairments are typically exacerbated when patients are required to conduct sequential movements using internal cues (i.e., planned programmed responses) to guide movement. We also documented progressive motor slowing in PD patients (8), which was most evident when visual information was reduced at high levels in advance of the patients' own moves.

Whereas Bradshaw et al. (17) investigated the incorporation and utilization of advance information during sequential movements by HD patients, our experiment examined their reliance on advance information; indeed, we suspect that inconsistencies in the literature may reflect the operation of such distinctions. In particular, we sought to determine the extent to which HD patients may rely on advance visual information to program and sequence motor programs. We (8) developed a serial choice button-pressing procedure that can independently assess two indices of response time—button "down time" (DT) and "movement time" (MT). The first, DT, is thought partly to reflect preparation time, as it measures how long each button is held down before initiating a move to the next button in the sequence. The second, MT, reflects execution time, as it measures the time "in-flight" between the release of one button and the depression of the next. This task enables a series of illuminated lights to be designated along a response board, and, with each successive button press, visual information (i.e., advance information about the pathway ahead) can be systematically reduced by extinguishing lights, to various extents, in advance of each successive move. Moreover, this task, which involves sequential forced-choice responding, also permits measurement of any progressive slowing as the se-
quence is traversed, as a function of how advance information is reduced. We predicted that HD patients would have difficulties in initiating and executing movements with high levels of reduction in advance information, that is, when they have to plan strategies of execution independently in advance of their own movement. We also predicted that HD patients would progressively slow in response execution as they conducted movements down the board under high levels of reduction in advance information.

METHOD

Subjects

Twelve patients with HD and 12 age-matched controls with no history of neurological disorder participated. There were five male and seven female participants in each group, all of whom were right-handed, with a mean age of exactly 50 years for each group. Duration of HD ranged from 2 months to 10 years with a mean duration of 4 years. Severity of functional decline was assessed by a psychiatrist (E.C.), and patients fell into either stages I, II, or III of the disease (19). Clinical data for the HD group, including medication, are shown in Table 1. All subjects were screened for dementia using the Short Test of Mental Status (20). A one-way analysis of variance (ANOVA) showed that scores obtained for the two groups were significantly different, $F(1, 11) = 10.94, p < 0.01$. To assess depression in HD, the Mood Assessment Scale was administered (21). A one-way ANOVA showed that HD patients were significantly more depressed than controls, $F(1, 11) = 12.62, p < 0.01$. Measures of attention included the Trail Making A and B tests (22), and the Stroop Interference task (23), which presents color words written in conflicting-color inks. A two-way ANOVA was conducted to compare groups on the two tasks in the Trail Making test, namely A (ascending numbers alone) and B (ascending number and letters), which revealed a significant Group by Task interaction, $F(2, 22) = 28.40, p < 0.001$. Post hoc one-way ANOVAs showed that both groups differed significantly in their performance on both A, $F(1, 11) = 78.03, p < 0.001$, and B, $F(1, 11) = 79.23, p < 0.001$, indicating that the HD group was overall performing slower than the controls on both tasks. For the Stroop task, a one-way ANOVA revealed that HD patients had a significantly higher interference score than controls, $F(1, 11) = 4.45, p < 0.05$.

Apparatus

Mounted upon a response board (480 mm long by 100 mm wide) were two parallel rows of 10 target buttons (8). Each button was raised 20 mm from the board and was 13 mm in diameter (Fig. 1). Adjacent buttons were 30 mm apart, as were the rows themselves. In addition, two single buttons (S1, S2) were sequentially pressed to initiate the task, and a further single button (F) at the other end of the board was pressed to complete a trial. Each button was illuminated by a light-emitting diode (LED) set into its base. A computer recorded the time that each button was held down (down time,

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Duration of HD (yrs)</th>
<th>Depression score</th>
<th>Medication for HD</th>
</tr>
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<tr>
<td>1</td>
<td>60</td>
<td>M</td>
<td>5</td>
<td>23</td>
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<tr>
<td>2</td>
<td>47</td>
<td>F</td>
<td>8</td>
<td>3</td>
<td>Tranylcypromine</td>
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<tr>
<td>3</td>
<td>56</td>
<td>M</td>
<td>9</td>
<td>13</td>
<td>Dothiepin</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>M</td>
<td>2</td>
<td>1</td>
<td>Imipramine</td>
</tr>
<tr>
<td>5</td>
<td>43</td>
<td>F</td>
<td>7</td>
<td>4</td>
<td>Dothiepin</td>
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<tr>
<td>6</td>
<td>63</td>
<td>F</td>
<td>10</td>
<td>6</td>
<td>Imipramine</td>
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<tr>
<td>7</td>
<td>60</td>
<td>F</td>
<td>2</td>
<td>11</td>
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<tr>
<td>8</td>
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<td>F</td>
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<tr>
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<td>M</td>
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<td>11</td>
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<tr>
<td>10</td>
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<td>18</td>
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<td>12</td>
<td>40</td>
<td>M</td>
<td>3</td>
<td>7</td>
<td>Haloperidol</td>
</tr>
</tbody>
</table>

HD, Huntington's disease; haloperidol, neuroleptic medication; tranylcypromine, dothiepin, and imipramine, antidepressants; ranitidine, treatment of ulcers.

Patients 4, 5, 6, and 10 were unmedicated. Duration of HD for patients 9 and 11 is 3 and 2 months, respectively.
FIG. 1. Response board used in the experiment. Subjects began by pressing S1, then S2, followed by a sequence of 10 movements between successive pairs of buttons, finishing at F.

DT) and the time between the release of one button and the depression of the next (movement time, MT). It also determined the button sequence to be followed (i.e., the illuminated path) at the beginning of each trial.

Procedure

The board was positioned across the subjects' midline, with the two start buttons (S1 and S2) closest to the right side of the body. A pathway of illuminated lights was presented down the board, in which there were two-way choice points at each of the 10 sequential pairs of buttons. Subjects were instructed to press each illuminated button with the index finger of the right hand as quickly as possible. If a button was incorrectly pressed or was pressed twice, the trial was terminated, and the occurrence was recorded as an error. Data from such trials were not included in the analysis, and the trial was repeated. Advance information (i.e., external visual cues) was systematically reduced in advance of the next movement in one of three ways as the subjects progressed along the board: (a) with no reduction in external cues, the next illuminated button was extinguished as the current button was released (i.e., no button extinguished in advance); (b) with moderate reduction, the next button was extinguished as the current button was depressed (i.e., one button extinguished in advance); and (c) with a high level of reduction in advance information, in addition to the next button remaining extinguished, the next-but-one button also extinguished as the current button was released.

There were eight different equidistant pathways in which the numbers of linear and diagonal move-
ments between successive button pairs were balanced, so that overall, the total distance in each movement sequence was invariant. These pathways were pseudorandomly presented across each of the three conditions, so that subjects could not predict the upcoming pathway. The different conditions were counterbalanced across subjects, with 16 experimental and six practice trials for each of the three external cue conditions.

RESULTS

Down Time

Figure 2 shows DT plotted as a function of Reduction in Advance Information for each group. The data were submitted to a mixed two-way ANOVA (Group, Reduction in Advance Information). There was a significant main effect of Group, $F(1, 22) = 37.52$, $p < 0.001$, a significant main effect of Reduction in Advance Information, $F(1, 22) = 11.65$, $p < 0.001$, and a highly significant interaction of Group by Reduction in Advance Information, $F(2, 44) = 10.69$, $p < 0.001$. Post hoc one-way ANOVAs and Tukey tests showed no significant differences for controls between any of the three levels of reduction in advance information, whereas HD patients showed significant ($p < 0.01$) differences between high (230 ms) and both moderate (189 ms) and no (176 ms) reduction, but no significant differences between moderate and no reductions.

Movement Time

Figure 2 also provides MT data. Once again there was a significant main effect of Group, $F(1, 22) = 43.13$, $p < 0.001$, a significant main effect of Reduction in Advance Information, $F(1, 22) = 8.15$, $p < 0.001$, and a significant interaction of Group by Reduction in Advance Information, $F(2, 44) = 3.33$, $p < 0.05$. Post hoc one-way ANOVAs and Tukey tests showed no significant differences for controls between any of the three levels of reduction in advance information, whereas HD patients showed significant ($p < 0.05$) differences between high (377 ms) and both moderate (327 ms) and no (329 ms) reduction in advance information but no significant differences between moderate and no reductions.

Sequencing Effects

To determine if there was any progressive slowing across the 10 sequential response locations, trend analyses were conducted for both DT and MT. For DT, there was a significant main effect of Sequence, $F(9, 360) = 4.30$, $p < 0.001$, which had a significant ($p < 0.001$) linear component, and a significant interaction of Group by Sequence, $F(9, 720) = 4.51$, $p < 0.001$ (Fig. 3). The highly significant three-way interaction of Group by Sequence by Reduction in Advance Information, $F(18, 720) = 1.33$, $p < 0.001$, indicates that whereas controls initiated movements in a similar fashion across the board for each of the three levels of reduction, these effects were very different for HD patients, who slowed progressively down the board with a high level of reduction in advance information.

For MT, similar results were found. There was a significant main effect of Sequence, $F(9, 360) = 7.24$, $p < 0.001$, which had a significant ($p < 0.001$) linear component, and an almost significant interaction of Group by Sequence, $F(9, 720) = 1.76$, $p < 0.07$ (Fig. 3). The highly significant three-way interaction of Group by Sequence by Reduction in Advance Information, $F(18, 720) = 2.87$, $p < 0.001$, indicates that whereas controls exhibited uniform MTs across the board with each of the three levels of reduction, HD patients displayed difficulty in progressively executing movements with the most reduced level of advance information.

Errors

The error rate for both groups increased for high levels of reduction in advance information, as compared to the other two conditions; this effect was most pronounced in the HD data. The median errors for the three conditions (no, moderate, high) for HD patients were, 2, 4, and 13, respectively, and for controls were, 0, 2, and 4, respectively. Mann-Whitney U tests conducted on the error data showed that there was a significant ($p < 0.05$) difference between the two groups only with high levels of reduction in advance information. Wilcoxon matched-pair tests showed that, for both groups, there were significant ($p < 0.05$) increases in errors with high levels of reduction in advance information. Because HD patients became slower and made more errors, we can therefore conclude that the DT and MT effects did not stem from any speed/accuracy trade-off.

Medication Types

The question whether medication may have affected HD performance must be addressed. Because four patients were taking neuroleptic medication, four were taking antidepressants, and four were unmedicated, we conducted a mixed three-way ANOVA for both DT and MT (neuroleptic, antidepressants, unmedicated vs. no, moderate,
and high levels of reduction) to determine whether or not performance across the three conditions was differentially affected by medication (Fig. 4).

For DT, there was of course a main effect of Reduction in Advance Information, $F(2, 18) = 11.39, p < 0.001$, no main effect of Group, and no significant interaction. For MT, there was a significant main effect of Reduction in Advance Information, $F(2, 18) = 6.53, p < 0.01$, no main effect of Group, and again no significant interaction. Consequently the shape of the function is not substantially altered by the nature of the medication or even its absence, and irrespective of medication, HD patients were uniformly disadvantaged with high levels of reduction in advance information.

Depression

The absence of any effect of depression on DT and MT for HD patients can be seen from Fig. 5. Yesavage et al. (21) stated that the cut-off for depression is 10 and above (of a maximum of 30). The propinquity of the data points renders unnecessary any further statistical treatment.

Trail Making Performance

The Trail Making test (22), which assesses frontal sequencing and attentional functions, had sharply discriminated between patients and controls. Consequently Pearson product–moment correlations were conducted between both parts and each of the three cue conditions of DT and MT; however, no correlations were significant. In any case, the nonsignificant correlations for high reduction in advance information for each of parts A and B for DT were +0.48 and +0.19, respectively, and for MT were +0.44 and +0.45, respectively. It is therefore unlikely that performance on this cognitive measure greatly influenced motor performance.

Stroop Interference Task

The Stroop Interference task (23), which also assesses frontal and attentional functions, had also sharply discriminated between patients and controls. Consequently Pearson product–moment correlations were conducted between the scores obtained on this task and each of the three cue conditions of DT and MT; however, no correlations were significant. The nonsignificant correlations for high reduction in advance information for both DT and MT were −0.29 and −0.53, respectively. Once again, performance on this cognitive measure is unlikely to influence greatly motor performance.
Short Test of Mental Status

The overall Short Test of Mental Status (20) score showed that HD patients were significantly more cognitively impaired than were controls. To determine any possible confounding influence of this impairment on motor performance, Pearson product-moment correlations were conducted between the scores obtained on this task and each of the three cue conditions of DT and MT. Again, no correlations approached significance. The nonsignificant correlations for high reduction in advance information for both DT and MT were +0.06 and −0.08, respectively. Therefore motor performance is not simply a product of mental status.

DISCUSSION

We have previously documented that HD patients experience problems in using advance information and in incorporating it into a motor program (17). In this study, we examined HD patients' reliance on visual cues, enabling us to compare findings with previously documented deficits in patients with PD (8). As predicted, HD patients as compared to controls had considerable difficulty in initiating and executing movements with high levels of reduction in advance information, as indicated by the increases in both DT and MT. For HD patients, whereas there was no significant increase in DT or MT between no and moderate levels of reduction, there were, however, significant increases in both the DT and MT data between moderate and high, and of course, between no and high levels of reduction in advance information. Control subjects' performance, on the other hand, remained completely constant across each of the three conditions, for both DT and MT. In particular, under conditions of maximum reduction, unlike PD patients (8) who only slowed with MT, HD patients progressively slowed with each successive element in the response sequence for both DT and especially MT. The difficulty patients experienced with the most reduced level of advance information is also reflected in an increased error rate. Moreover, medication (its presence, or type) failed to affect the pattern of results, an observation that was also reported by Thompson et al. (10). Moreover, performance on various cognitive measures (e.g., Trail Making Test A and B, Stroop Interference Task, and the Short Test of Mental Status) failed to correlate with motor performance. Our main findings, therefore, are not likely to be simply a product of the patients' cognitive status.

HD patients are known to exhibit deficits in long-term procedural as well as declarative memory (24–25).
However, we would not expect any contribution to our findings from a deficit at either level, as the pathway was not a learned sequence, and no retention interval (especially for high levels of reduction in advance information) ever exceeded 1 s.

HD, as well as PD, patients experience difficulties in both initiating and in executing movements with limited visual guidance. Previous studies (10,12–14,16,17), indicated that MT may be a more sensitive indicator of HD; however, in our study, DT effects did not differ greatly from those of MT.

Disturbances of voluntary movement (i.e., akinesia and bradykinesia) are useful indicators of HD functioning. Indeed, DT (reflecting akinesia) and especially MT (reflecting bradykinesia) progressively increased with each successive element in the response sequence with high levels of reduction in advance information. Contrary to our findings, Agostino et al. (16) reported that PD, but not HD, patients progressively slowed in their execution of complex motor programs. However, the repetitive sequential movements employed by those authors consisted of drawing different geometrical patterns in a counterclockwise direction, the patterns being formed by two, three, four, and five segments of identical length. Discrepancies in findings between the two studies may well reflect differing levels of movement uncertainty.

It may be the case that HD (like PD) patients rely heavily on external visual cues to guide movement (9). With no reduction in advance information, prior programming and movement planning may be optimally realized, because patients can rely on external visual cues to initiate and execute motor programs. With high levels of reduction in advance information, however, movements need to be planned and programmed in advance, as the target path disappears from view ahead of each next move. With limited visual guidance, HD patients may require more time to plan each next submovement, and as a consequence, become less effective in using already compromised internal switching mechanisms to sequence movements progressively down the board (29).

As a subject prepares to initiate a predictable, well-learned response, tonic activity builds up over the supplementary motor area (SMA), and, at release of the response, is terminated by phasic activity (an internally generated "cue") from the globus pallidus (30–32), the output circuit of the BG. Consequently, the difficulty experienced by HD patients in switching between motor segments, and in
planning movements ahead of time with the most reduced level of advance information, may be partly explained by defective internal cueing (i.e., defective phasic pallidal activity) within the BG. Thus when external cues were maximally reduced in our procedure, even though the pathway was not, of course, a learned sequence per se, subjects had to maintain and continuously update an internal representation of each next pair of moves, which had previously extinguished. This BG-SMA system for mediating such an internally represented sequence is known to be compromised in PD and may well be similarly damaged in HD. Quite separately from this putative deficit, prefrontal involvement in planning movements ahead of time with the most advance information is therefore also likely to further disadvantage the already compromised premotor area. Either or both of these mechanisms could explain our findings.

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