Behavioural abnormalities contribute to functional decline in Huntington’s disease


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The independent and relative contributions of motor, cognitive, and behavioural deficits to functional decline in patients with Huntington’s disease are examined. Twenty-two patients with Huntington’s disease were assessed with rating scales for motor dysfunction, cognitive measures of executive functions, and behavioural measures of apathy, executive dysfunction, and disinhibition. Their functional status was assessed with informant based and clinician based ratings of activities of daily living (ADL). A composite apathy/executive dysfunction behavioural index was strongly related to decline in ADL independently and after controlling for motor and cognitive deficits. These results suggest that behavioural dysfunction contributes to functional decline in patients with Huntington’s disease and may impede their ability to utilise motor or cognitive skills that remain available in the early stages of the disease.

Huntington’s disease is a genetically transmitted neurodegenerative disease that results in a severe movement disorder (chorea, dystonia, bradykinesia, and oculomotor deficits) because of atrophy of the basal ganglia and related brain structures. The movement disorder is accompanied by notable cognitive impairment (for example, executive dysfunction) and behavioural changes such as depression, irritability, apathy, and inflexibility. In some combination, the triad of motor, cognitive, and behavioural deficits associated with Huntington’s disease contributes to profound functional decline with a gradual loss of independence in performing the usual activities of daily living (ADL).

Previous studies have shown that the severity of functional impairment in patients with Huntington’s disease is at least moderately related to the severity of their motor and cognitive dysfunction. However, these factors account for only a portion of the variance in ADL decline, and additional variance might be explained by the behavioural abnormalities that occur in the disease. The profound apathy, lack of initiative, and irritability shown by some patients with Huntington’s disease may interfere with their ability to perform certain ADL even though they retain the necessary motor and cognitive capacity.

To address this issue, we examined the relation between functional disability and motor, cognitive, and behavioural deficits in individuals with Huntington’s disease. We hypothesised that disease related changes in behaviour would significantly influence ratings of functional capacity even after the effects of motor and cognitive deficits were taken into account.

METHODS

Participants

The participants were 22 patients with Huntington’s disease (13 women, 9 men) who had an informant available to complete behavioural and functional ratings. All patients were recruited from the Huntington’s Disease Centers of Excellence at the University of California, San Diego (UCSD) (n = 16) or the University of Iowa (n = 6). The institutional review boards at each institution approved all the procedures. Written consent was obtained from the participants after the study was fully explained to them.

The subjects had a positive family history of Huntington’s disease or a positive genetic test for the mutation, and presented with at least one major neurological sign of the disease (chorea or dystonia) on the unified Huntington’s disease rating scale (UHDRS). Mean (SD) age of the participants was 46.3 (8.4) years, and they had 13.9 (2.0) years of education, an estimated premorbid IQ of 112.5 (9.9), and a Mattis dementia rating scale (DRS) score of 120.0 (13.2), which is indicative of mild to moderate dementia. English was the first language of all the patients. Most were classified as having no (n = 12) or minimal (n = 4) depressive symptoms, according to the Beck depression inventory (BDI); however, a subset had mild to moderate (n = 2), moderate to severe (n = 1), or severe (n = 3) depressive symptoms. Many of the patients were taking antidepressants (n = 12), neuroleptics (n = 7), anticonvulsants (n = 4), or anxiolytics (n = 3), either alone or in combination. No patient had a reported history of stroke, brain tumour, brain surgery, head injury with loss of consciousness for more than five minutes, or substance abuse/dependence within the past year.

Procedures

Motor assessment

The severity of motor dysfunction was assessed using the motor examination from the UHDRS. Total scores range between 0 and 124, with higher scores signifying greater motor dysfunction.

Cognitive testing

The pattern recognition, spatial recognition, spatial span, and spatial working memory subtests of the Cambridge neuropsychological test automated battery (CANTAB) were administered according to the standard test protocol. A CANTAB cognitive composite score was derived by computing z scores for each of the four subtests and averaging across the four scores. The controlled oral word association test and the symbol digit modalities test of the UHDRS were also administered and a composite UHDRS cognitive z score derived.

Abbreviations: ADL, activities of daily living; BDI, Beck depression inventory; CANTAB, Cambridge neuropsychological test automated battery; FLOPS, frontal lobe personality scale; HD-ADL, Huntington’s disease activities of daily living scale; TFC, total functional capacity scale; UHDRS, unified Huntington’s disease rating scale
The frontal lobe scale (FLOPS) was completed by a clinician. The HD-ADL scale was divided into separate instrumental (for example, communication, finances) and physical (eating, dressing) ADL subscales. The Shoulson–Fahn instrumental (for example, communication, finances) and composite score (mean z score = −2.0 (1.1)), the TFC (mean = 8.7 (3.9)), and instrumental (mean = 60.6 (28.3%)) and physical (mean = 77.3 (22.6%)) HD-ADL scores were indicative of mild to moderate impairment. Change scores for the FLOPS subscales differed significantly from zero (p values < 0.001; indicating worsening behaviour), with the apathy score (mean = 1.2 (0.7)) greater than the executive dysfunction score (mean = 0.9 (0.7); p < 0.05) and the executive dysfunction score greater than the disinhibition score (mean = 0.5 (0.5); p < 0.01). For remaining analyses apathy and executive dysfunction subscales were combined because they were highly correlated (r = 0.83, p < 0.001).

The disinhibition subscale was not significantly correlated with any of the three functional measures (instrumental HD-ADL, r = −0.17; physical HD-ADL, r = 0.07; TFC, r = 0.09). In contrast, the apathy/executive score was highly related to the scores obtained on the instrumental HD-ADL (r = −0.92), the physical HD-ADL (r = −0.83), and the TFC (r = −0.77) functional measures (all p values < 0.001; fig 1).

Multiple regression analyses showed that a combination of the motor score, the CANTAB cognitive score, and the apathy/executive score accounted for 91% of the variance in the instrumental HD-ADL score (adjusted $R^2 = 0.90$; p < 0.001), 83% of the variance in the physical HD-ADL score (adjusted $R^2 = 0.80$; p < 0.001), and 82% of the variance in TFC score (adjusted $R^2 = 0.79$; p < 0.001).

The unique variance in function explained by each variable was then determined after controlling for the variance accounted for by both of the other two variables (table 1). The apathy/executive score accounted for significantly more unique variance in the instrumental HD-ADL scores than did the motor score (36% v 3% (95% confidence interval 6% to 63%)) or the CANTAB cognitive score (36% v < 1% (9% to 67%)). There was no significant difference in the percentage of variance in physical HD-ADL or TFC scores explained by the behavioural, motor, and cognitive scores.

Similar multiple regression analyses using the UHDRS cognitive score instead of the CANTAB cognitive score showed that the motor score, the cognitive score, and the apathy/executive score accounted for 92% of the variance in the instrumental HD-ADL score (adjusted $R^2 = 0.90$; p < 0.001), 84% of the variance in the physical HD-ADL score (adjusted $R^2 = 0.81$; p < 0.001), and 84% of the variance in TFC score (adjusted $R^2 = 0.81$; p < 0.001). Additional analyses showed that the apathy/executive score accounted for significantly more unique variance (table 1) in the instrumental HD-ADL scores than did the UHDRS cognitive score (18% v 1% (3% to 37%)). No other comparisons were significantly different.

**DISCUSSION**

Our results show that a composite behavioural index of apathy/executive dysfunction in patients with Huntington’s disease is strongly related to informant based or clinician based ratings of decline in their everyday activities. This behavioural measure accounted for a significant amount of unique variance in the ADL measures even after controlling for the effects of motor and cognitive deficits, and this remained the case even if instrumental or physical ADL were considered separately. Thus behavioural dysfunction may be quite disabling in patients with Huntington’s disease and could impede their ability to utilise motor or cognitive skills that may still be available in the early stages of the disease.

Apathy was the most significant behavioural abnormality to develop in patients with Huntington’s disease, consistent with a previous finding of apathy in roughly 50% of affected patients who were assessed with the neuropsychiatric inventory. This does not appear to be a reflection of depression as there was no significant relation between scores on the BDI and the FLOPS apathy subscale (or any other subscale) in the present study (r = 0.18, p > 0.4) or in a previous

![Figure 1](http://jnnp.bmj.com/) Scatterplots showing the relation between the apathy/executive dysfunction composite change ratio (apathy/executive score) and percentage scores on the Huntington’s disease activities of daily living (HD-ADL) instrumental (top) and physical (middle) subscales and the total functional capacity scale (bottom).

**Results**

Values are given as mean (SD) throughout. The average UHDRS motor score (mean = 29.9 (20.8)), the CANTAB composite score (mean z score = −1.5 (1.3)), the UHDRS composite score (mean z score = −2.0 (1.1)), the TFC (mean = 8.7 (3.9)), and instrumental (mean = 60.6 (28.3%)) and physical (mean = 77.3 (22.6%)) HD-ADL scores were indicative of mild to moderate impairment. Change scores for the FLOPS subscales differed significantly from zero (p values < 0.001; indicating worsening behaviour), with the apathy score (mean = 1.2 (0.7)) greater than the executive dysfunction score (mean = 0.9 (0.7); p < 0.05) and the executive dysfunction score greater than the disinhibition score (mean = 0.5 (0.5); p < 0.01). For remaining analyses apathy and executive dysfunction subscales were combined because they were highly correlated (r = 0.83, p < 0.001).

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study with a larger sample of Huntington’s disease patients.12 Rather, the frontostriatal neuropathology that occurs in Huntington’s disease11 appears to lead to a primary reduction in drive and motivation that is manifested as behavioural apathy.

Conclusions

Behavioural dysfunction makes an important contribution to the decline in everyday functioning in patients with Huntington’s disease, and a full accounting of the antecedents of their functional decline must consider the interaction between motor, cognitive, and behavioural impairment. Although this conclusion must be generalised cautiously because of the relatively small sample size and the retrospective nature of the behavioural ratings, our results underscore the value of assessing behavioural change in Huntington’s disease.

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REFERENCES


Table 1 Unique variance in function explained by performance on the behavioural, cognitive, or motor measure after controlling for the variance accounted for by performance on both of the other two measures ($R^2$ change)

<table>
<thead>
<tr>
<th>Measures</th>
<th>HD-ADL scale</th>
<th>UHDRS</th>
<th>TFC scale</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Instrumental activities: $R^2$ change (95% CI)</td>
<td>Physical activities: $R^2$ change (95% CI)</td>
<td>$R^2$ change (95% CI)</td>
</tr>
<tr>
<td>Apathy/executive</td>
<td>36.0% (9% to 67%)*</td>
<td>22.0% (2% to 30%)</td>
<td>13.0% (0.4% to 41%)</td>
</tr>
<tr>
<td>UHDRS motor score</td>
<td>3.0% (0% to 9%)†</td>
<td>5.0% (0.2% to 17%)</td>
<td>12.0% (0.4% to 26%)</td>
</tr>
<tr>
<td>Apathy/executive</td>
<td>18.0% (5% to 38%)*</td>
<td>12.0% (2% to 30%)</td>
<td>6.0% (0.1% to 21%)</td>
</tr>
<tr>
<td>UHDRS-cognitive</td>
<td>1.0% (0% to 3%)</td>
<td>1.0% (0% to 5%)</td>
<td>&lt;1.0% (0% to 5%)</td>
</tr>
<tr>
<td>Motor</td>
<td>5.0% (1% to 13%)</td>
<td>8.0% (1% to 17%)</td>
<td>19.0% (4% to 32%)</td>
</tr>
</tbody>
</table>

*Apathy/executive score accounted for significantly more variance in the functional score than the cognitive variables.
†Apathy/executive score accounted for significantly more variance in function score than the UHDRS motor score.

CANTAB-cognitive, cognitive component of the Cambridge neuropsychological test automated battery; CI, confidence intervals determined by a bootstrap procedure; UHDRS, unified Huntington’s disease rating scale; UHDRS-cognitive, cognitive component of the UHDRS.