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Depressive Symptom Severity is Related to Poorer Cognitive Performance in Prodromal Huntington Disease

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Abstract

Objective—Depression is associated with more severe cognitive deficits in many neurological disorders, though the investigation of this relationship in Huntington disease (HD) has been limited. This study examined the relationship between depressive symptom severity and measures of executive functioning, learning/memory, and attention in prodromal HD.

Method—Participants (814 prodromal HD, 230 gene-negative) completed a neuropsychological test battery and the Beck Depression Inventory-II (BDI-II). Based on the BDI-II, there were 637 participants with minimal depression, 89 with mild depression, 61 with moderate depression, and 27 with severe depression in the prodromal HD group.

Results—ANCOVA (controlling for age, sex, and education) revealed that performance on SDMT, Trails B, HVLT-R Immediate Recall, and Stroop interference was significantly different between the BDI-II severity groups, with the moderate and severe groups performing worse than the minimal and mild groups. There were no significant differences between the BDI-II severity groups for Trails A or HVLT-R Delayed Recall. Linear regression revealed that both gene status and depression severity were significant predictors of performance on all cognitive tests examined, with contributions of BDI-II and gene status comparable for Trails A, SDMT, and Stroop interference. Gene status had a higher contribution for HVLT-R Immediate and Delayed Recall and Trails B.

Conclusions—Our results suggest that depressive symptom severity is related to poorer cognitive performance in individuals with prodromal HD. Though there are currently no approved therapies for cognitive impairment in HD, our findings suggest that depression may be a treatable contributor to cognitive impairment in this population.

Keywords

Huntington disease; depression; cognitive impairment; neuropsychology

Depression has been consistently linked with cognitive deficits in many neurological disorders. The etiology of depression in these disorders is likely multiply determined. While the relationship between depression and cognition has been explored in neurodegenerative diseases such as Parkinson disease (PD) and multiple sclerosis (e.g. Arnett et al., 1999;

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Troster et al., 1995), the investigation of this relationship in Huntington disease (HD) has been limited.

HD is an autosomal-dominant neurodegenerative disorder caused by a trinucleotide repeat expansion (CAG) resulting in progressive motor, cognitive, and psychiatric symptoms. Depression commonly occurs in HD with prevalence estimates around 40–50% (Duff, Paulsen, Beglinger, Langbehn, & Stout, 2007; Epping & Paulsen, 2011). While overall, there is evidence the prevalence of depression *decreases* with disease progression, depressive severity tends to wax and wane (Paulsen et al., 2005) and does not correlate with CAG repeat length (Zappacosta et al., 1996).

Previous literature examining the relationship between depression and cognition in HD has been equivocal. The typical cognitive profile in HD includes prominent impairments in attention, executive functioning, and memory (Paulsen et al., 1995). Results of some prior studies have indicated that depression and cognitive impairment are not significantly correlated in patients with manifest HD (Thompson, Snowden, Craufurd, & Neary, 2002; Zappacosta et al., 1996). Further, Lundervold and Reinvang (1991) found that depression scores were lower for participants with severe cognitive impairment due to HD than for participants with mild or moderate impairment. However, the literature reviewed has generally included participants with significantly progressed HD, in which case a subtler effect may be missed or the accuracy of reporting of depression may be affected.

The influence of depression on cognition in individuals who have tested positive for the gene expansion, but who do not yet meet the criteria for manifest HD, is not well understood. Though clinical diagnosis of HD is based on the emergence of characteristic motor symptoms (Huntington Study Group, 1996), cognitive and psychiatric changes begin well before formal diagnosis (Duff et al., 2007; Paulsen et al., 2006; Stout et al., 2011). Individuals who are positive for the gene expansion but who have not yet met criteria for a motor diagnosis are described as being in the prodromal phase of HD (Paulsen et al., 2006; Paulsen et al., 2008). Despite negative findings in diagnosed HD, depression may be related to poorer cognitive test performance in prodromal HD.

To our knowledge, the only previous investigation of the relationship between depression and cognitive impairment in prodromal HD was conducted by Nehl, Ready, Hamilton, and Paulsen (2001) in 15 participants with prodromal HD. Using measures from the Cambridge Neuropsychological Test Automated Battery (Sahakian & Owen, 1992), they found that an aggregated measure of depressive symptoms (made up of the depression item from the Unified Huntington's Disease Rating Scale and the Beck Depression Inventory) was a significant predictor of performance on a spatial working memory task with higher depression scores related to poorer performance. There was no significant relationship between depression and visual memory. More recently, Duff et al. (2007) included an analysis of the relationship between ratings on the Symptom Checklist-90-Revised and performance on the Symbol Digit Modalities Test in the context of a larger investigation of psychiatric symptomatology in prodromal HD and found that higher levels of psychopathology were associated with poorer cognitive performance. As noted by Nehl et al. (2001), it is important to understand the relationship between depression and cognition in prodromal HD because there are effective treatments for depression, but, as yet, no effective treatments for impaired cognition. However, prior studies have suffered from small sample sizes and limited measures of cognition. We hypothesized that, when tested with sensitive measures of executive functioning, learning and memory, and attention, participants with significant depressive symptoms and prodromal HD would demonstrate poorer performance on cognitive measures when compared with participants with minimal or no depressive symptoms and prodromal HD. Further, we expected that gene status and depression would

make individual contributions to the prediction of cognitive performance when participants with prodromal HD were compared to controls.

Method

Participants

Data for this investigation were collected from October 2002 to October 2009 from participants in PREDICT-HD, an ongoing, multisite, prospective, longitudinal study of neurobiological and behavioral changes in individuals at risk for HD who have not yet evidenced motor signs required for diagnosis (Paulsen et al., 2006; Paulsen et al., 2008). Participants' baseline data were analyzed in the current manuscript. All participants had completed genetic testing for HD prior to (and independent from) study enrollment. To enroll in PREDICT-HD, participants were required to be 18 years of age or older and could not yet be diagnosed with manifest HD. Exclusion criteria included history of a significant developmental cognitive disorder, other CNS disease or injury, evidence of an unstable medical or psychiatric illness (including substance abuse), a pacemaker or metallic implants, or having taken prescribed antipsychotic medication in the last 6 months or phenothiazine derivative antiemetic medication in the 3 months prior to enrollment. All participants provided informed consent (reviewed and approved by the Institutional Review Board at their respective sites) and were treated in accordance with the ethical standards of the American Psychological Association. Participants consisted of 296 men (36.36%) and 518 women (63.64%) in the prodromal HD group (CAG repeats ≥ 36) and 85 (36.96%) men and 145 (63.04%) women in the comparison group (CAG repeats < 36) for a total of 1,044 participants. Due to our focus on depression and its relationship with cognition in prodromal HD, the comparison group was not included in the primary analyses.

Procedure

Participants completed a neuropsychological test battery, the Beck Depression Inventory-II (Beck, Steer, & Brown, 1996), and the Unified Huntington's Disease Rating Scale (Huntington Study Group, 1996). The motor assessment was completed by certified motor raters while all other measures were administered by trained research personnel. All cognitive measures were completed based on manual instructions.

Measures

The Beck Depression Inventory-II (BDI-II) is a 21-item, self-rated measure for assessing depressive symptoms (Beck et al., 1996). The manual states that higher scores indicate more severe depressive symptoms with scores 0-13 indicating minimal depression, scores 14–19 indicating mild depression, scores 20–28 indicating moderate depression, and scores 29–63 indicating severe depression.

Cognitive Measures

Measures sensitive to early cognitive changes in prodromal HD (Stout et al., 2011) and cognitive impairment associated with depression in comparable literatures (e.g., Parkinson disease (Stefanova et al., 2006)), were selected a priori (to avoid multiple comparisons) from a larger battery. The Symbol Digit Modalities Test (SDMT) (Smith, 1982) measures working memory, complex scanning, and processing speed. Raw scores indicate the number of items correctly completed in 90 seconds. The Trail Making Test (Reitan, 1958) includes Trails A (TMT-A) and B (TMT-B). TMT-A is a measure of visual scanning, psychomotor speed, and speeded attention. TMT-B also requires set-shifting and maintenance. Raw scores indicate the number of seconds required to complete each test. The interference trial of the Stroop Color-Word test (Stroop, 1935) requires consistent inhibition of an overlearned

response. Raw scores indicate the number of items correctly completed in 45 seconds. The Hopkins Verbal Learning Test-Revised (HVLT-R) (Brandt & Benedict, 1991) is a word list learning test that includes immediate (total words recalled over three trials) and delayed recall indices. Raw scores indicate number of words recalled.

Data Analytic Strategy

One-way, between subjects ANOVA and ANCOVA were used to evaluate differences among the BDI-II groups, cognitive variables, and most demographic variables. Chi square tests for independence were used to examine differences between groups on categorical variables. Pearson correlations were used to determine the nature of the relationship between BDI-II scores and Unified Huntington's Disease Rating Scale (UHDRS) total motor scores. Multiple linear regression analyses were used to examine the individual contributions of gene status and depression to cognitive performance. Because the scores for TMT-A and TMT-B were not normally distributed, they were log-transformed to induce greater symmetry in the residuals.

Results

Demographic, Mood, and Neuropsychological Characteristics of the Groups

We first examined depressive symptoms in participants with prodromal HD. Based on manual cut-offs for the BDI-II, there were 637 participants with minimal depression (mean BDIII score= 4.24, SD= 3.92), 89 with mild depression (mean BDI-II score= 16.30, SD= 1.84), 61 with moderate depression (mean BDI-II score= 23.21, SD= 2.67), and 27 with severe depression (mean BDI-II score= 36.11, SD= 6.39). Chi-square test revealed a relationship between gender and depression severity ($\chi^2 = 14.54$, df = 3, $p < .005$), with females overrepresented in the mild (60% female), moderate (79% female), and severe (78% female) depression groups. ANOVA revealed that the minimal depression severity group had a higher mean age ($F_{(3, 810)} = 4.95$, $p < .005$) than the mild, moderate, and severe groups. The groups also were significantly different on years of education ($F_{(3, 810)} = 3.16$, $p < .05$), with the minimal depression group significantly higher than the severe group. Differences were found on the UHDRS motor score ($F_{(3, 809)} = 5.17$, $p < .005$), with the minimal group scoring significantly lower than the moderate and severe groups and the mild group scoring significantly lower than the moderate group. BDI-II scores and UHDRS total motor scores were significantly correlated (r = .14, $p \leq .0001$). The participants with prodromal HD were compared to the gene expansion negative participants on age, years of education, and gender. The prodromal HD group had a mean age of 40.62 (SD = 9.86) and mean years of education of 14.32 (SD = 2.67), and the gene expansion negative group had a mean age of 43.60 (SD = 11.62) and mean years of education of 14.70 (SD = 2.63). The groups were significantly different based on age ($F_{(1, 1042)} = 15.02$, $p \leq .0001$), but not on years of education ($F(1, 1042) = 3.10$, $p = .0788$), or gender ($\chi^2 = 0.027$, df = 1, $p = .869$).

Primary data analyses

Analysis of covariance (ANCOVA) was used to examine differences among the BDI-II groups in cognitive performance. Covariates for all tests were age, gender, and years of education. There were no significant differences between the BDI-II severity groups for TMT-A ($F_{(3, 802)} = 1.84$, $p = .1379$) and HVLT-R Delayed Recall ($F_{(3, 805)} = 2.43$, $p = .0643$). However, performance on SDMT ($F_{(3, 806)} = 6.79$, $p < .0005$), TMT-B ($F_{(3, 794)} = 5.27$, $p < .005$), HVLT-R Immediate Recall ($F_{(3, 806)} = 3.37$, $p < .05$), and Stroop Interference ($F_{(3, 804)} = 3.11$, $p < .05$) were significantly different between the BDI-II severity groups (see Table 1). When examining comparisons between the groups, for the SDMT, the minimal and mild groups performed significantly better than the moderate group ($p \leq .0001$; $p < .05$, respectively). For TMT-B, the minimal group performed significantly

better than the moderate group ($p \leq .001$) and the severe group ($p < .05$). For HVLT-R Immediate Recall, the minimal group performed significantly better than the moderate group ($p < .05$) and the severe group ($p < .05$). On Stroop Interference, the minimal group performed significantly better than the moderate group ($p < .05$).

Secondary data analyses

To examine whether depression or prodromal HD status has more of an impact on cognition, control participants were included in separate linear regression analyses with each cognitive score serving as the dependent variable and group membership (prodromal HD vs. control) and BDI-II score serving as predictors (adjusting for age, sex, and years of education in all analyses). Overall, both gene mutation status (positive/negative) and depression significantly contribute to cognitive performance. However, the effect of depression was either equivalent to or less than the effect of group membership. Qualitatively, the contributions of depression and group membership accounted for similar proportions of variance in TMT-A, SDMT, and Stroop performances (see Table 2). Group membership accounted for more variance than depression for HVLT-Immediate Recall, HVLT-Delayed Recall, and TMT-B performances. Gene status group by BDI-II score interactions were tested, but results failed to reach significance.

Discussion

In our large sample of participants with prodromal HD, participants with significant depression (i.e. those with moderate to severe depression) demonstrated worse performance on four of the six cognitive measures examined. Further, depression and group status (i.e., gene mutation negative vs. positive) have independent, significant contributions to cognitive performance. Our results replicate and extend those of Nehl et al. (2001) in a much larger and independent sample, suggesting that depression is associated with performance on several cognitive tasks. Not only do the depression severity groups demonstrate statistically significantly different performances, these differences also appear to be clinically significant. For example, the moderately depressed group scored 1.35 standard deviations below the mean for females 30– 39 years of age with > 12 years of education based on SDMT norms (Sheridan et al., 2006). While 1.5 standard deviations below the normative group mean is a more widely accepted cut off for determining cognitive impairment, there is precedent in both the Mild Cognitive Impairment (Delano-Wood et al., 2009) and HIV-Associated Neurocognitive Disorders (Woods, Moore, Weber, & Grant, 2009) literatures for interpretation of a more liberal guideline of 1 or 1.2 standard deviations below the mean.

It is important to note that that there was not a consistent direct relationship between depression and cognition, in that the severe group performed better than the moderate group on the SDMT. This finding may reflect measurement issues of the BDI-II at the severe end of the scale in this population or the smaller sample size in the most severely depressed group.

No relationship was found between depression and cognitive performance for TMT-A or HVLT-Delayed Recall. It may be that an effect was not seen for TMT-A because participants could still perform well on this task. To elaborate, the severely depressed group mean in our sample is roughly equivalent to the demographically appropriate normative group mean reported by Tombaugh (2004) (i.e., 28.54 vs. 28.44). However, an effect was found for TMT-B, on which the severely depressed group scored > 2.5 standard deviations below the mean relative to Tombaugh's norms. Scores > 1 standard deviation below the mean on TMT-B have been demonstrated to be related to greater activities of daily living impairment (Johnson, Lui, & Yaffe, 2007). In keeping with the findings of Hartlage et al. (1993) in depressed, but neurologically healthy individuals, it may be that the relationship

between depressive symptoms and poorer cognitive performance is more apparent in tasks requiring effortful, speeded processing. However, this justification cannot explain the HVLT-R results, in which the more significantly depressed participants performed in the low average range based on manual norms for both Immediate Recall (related to depression in this sample) and Delayed Recall (not related to depression in this sample) indices. This discrepancy may be due to the Immediate Recall score being a psychometrically more robust score given that it reflects performance across three learning trials, rather than the single delayed recall trial. Alternatively, it may be that in this sample, learning efficiency was more related to depression than recall.

These findings are encouraging in highlighting a potentially treatable contributor to cognitive dysfunction in prodromal HD. Future investigations may explore whether successful interventions for depression also result in improved cognition, though results are not promising in the literature for related conditions (Dobkin et al., 2010). Cognitive impairment may, in fact, serve as a predictor of poorer anti-depressant treatment response (Dobkin et al., 2010; Julian & Mohr, 2006). However, replication in HD populations is needed.

BDI-II scores and UHDRS motor scores were found to be significantly correlated, though the effect was small ($r = .14$). It may be that significant depression co-occurs with more rapid motor decline in prodromal HD, as has been demonstrated in PD (Starkstein, Mayberg, Leiguarda, Preziosi, & Robinson, 1992; Stefanova et al., 2006). However, this suggestion is speculative.

Limitations to our findings include the cross-sectional nature of the study design. Without temporality, we cannot discern whether depressive symptoms cause more significant cognitive impairment, whether cognitive impairment predisposes individuals with prodromal HD to develop depression, or whether depression and cognitive impairment co-occur due to similar underlying neuropathology. A longitudinal investigation of depression treatment including neuroimaging may better address the causal direction and neuropathological basis of these symptoms. Neuroimaging measures may also help elucidate whether severely depressed individuals with prodromal HD represent a subgroup with a particular pattern of neurodegeneration. The inclusion of participants who had not yet been diagnosed with HD may limit the generalizability of our results. As noted previously, it may be that once HD has significantly progressed and cognitive deficits are more pronounced, the nature of the relationship between depression and cognition changes. Another potential limitation is that our investigation relies on a self-report measure of depressive symptoms. Much remains to be learned regarding the validity of self-report scales in prodromal HD. However, underreporting of depressive symptoms in our sample would be more likely to occur in cognitively impaired participants, thereby underestimating the number of individuals with cognitive impairment in more depressed groups and biasing our results to the null. Apathy was not specifically assessed in this investigation. Future investigations including measures of motivation and apathy may better address their role in cognition in this population. Lastly, PREDICT-HD participants have opted to undergo predictive genetic testing, participate in research, and take part in yearly evaluations and therefore may not be completely representative of the larger prodromal HD population.

Despite previous investigations in participants with diagnosed HD that failed to find a link between depressive symptoms and more significant cognitive impairment, our results indicate that depressed participants with prodromal HD perform more poorly on tests of information processing, immediate verbal recall, speeded set shifting, and inhibition. The discrepancy between our results and findings in populations with diagnosed HD may be due to differences in the disease process as it advances (i.e., more subtle contributions of

depression may be more evident when cognitive impairment is still mild to moderate) and/or due to statistical power (i.e., with our very large sample, our study was more than adequately powered to detect a small to moderate effect). Our findings highlight the importance of close monitoring of depressive symptoms in individuals with prodromal HD. Because depression may also be an indicator of cognitive impairment, individuals with prodromal HD and depression may benefit from neuropsychological assessment to assist with treatment recommendations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Mean (standard deviation) of variables

Variable	BDI-II Severity Groups				*p*-value*
	Minimal (n = 637)	Mild (*n* = 89)	Moderate (*n* = 61)	Severe (*n* = 27)	
Age[a]	41.3 (10.00)	39.0 (9.33)	38.5 (8.72)	36.5 (8.06)	
Education[a]	14.45 (2.66)	14.16 (2.33)	13.89 (3.13)	13.04 (2.77)	
SDMT[1]	50.76 (11.54)	49.35 (11.96)	45.16 (10.71)	47.07 (10.63)	< .0005
TMT-B[2]	66.89 (31.31)	72.03 (45.67)	79.64 (41.50)	82.70 (47.00)	< .005
HVLT-IR[3]	26.37 (4.93)	26.19 (5.51)	24.85 (5.59)	24.00 (5.00)	< .05
Stroop[4]	44.89 (9.93)	44.12 (10.52)	42.13 (12.01)	41.15 (11.43)	< .05
TMT-A[5]	27.60 (11.08)	27.54 (9.90)	30.88 (15.11)	28.44 (10.32)	ns
HVLT-DR[6]	9.51 (2.27)	9.57 (2.35)	8.92 (2.70)	8.59 (2.42)	ns

[1] Symbol Digit Modalities Test,

[2] Trail Making Test-B,

[3] Hopkins Verbal Learning Test-Revised Immediate Recall,

[4] Stroop Interference,

[5] Trail Making Test-A,

[6] Hopkins Verbal Learning Test-Revised Delayed Recall

* *p*-values reported for omnibus F test, see text for df

[a] = Values given in years

Table 2

Regression results: partial r^2 values controlling for age, sex, and years of education

Dependent Variable	Gene Expansion Status[a]	BDI-II
SDMT[1]	.0215***	.0150***
TMT-A[2]	.0099**	.0098**
TMT-B[3]	.0165***	.0095**
HVLT-IR[4]	.0235**	.0088***
Stroop[5]	.0084**	.0079**
HVLT-DR[6]	.0096**	.0052*

[1] Symbol Digit Modalities Test,

[2] Trail Making Test-A,

[3] Trail Making Test-B,

[4] Hopkins Verbal Learning Test-Revised Immediate Recall,

[5] Stroop Interference,

[6] Hopkins Verbal Learning Test-Revised Delayed Recall

[a] = positive vs. negative

* $p < .05$,

** $p < .005$,

*** $p < .0001$