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Characterization of Depression in Prodromal Huntington Disease in the Neurobiological Predictors of HD (PREDICT-HD) Study

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Abstract

Depression causes significant morbidity and mortality, and this also occurs in Huntington Disease (HD), an inherited neurodegenerative illness with motor, cognitive, and psychiatric symptoms. The presentation of depression in this population remains poorly understood, particularly in the prodromal period before development of significant motor symptoms. In this study, we assessed depressive symptoms in a sample of 803 individuals with the HD mutation in the prodromal stage and 223 mutation-negative participants at the time of entry in the Neurobiological Predictors of HD (PREDICT-HD) study. Clinical and biological HD variables potentially related to severity of depression were analyzed. A factor analysis was conducted to characterize the symptom domains of depression in a subset (n=168) with clinically significant depressive symptoms. Depressive symptoms were found to be more prevalent in HD mutation carriers but did not increase with proximity to HD diagnosis and were not associated with length of the HD mutation. Increased depressive symptoms were significantly associated with female gender, self-report of past history of depression, and a slight decrease in functioning, but not with time since genetic testing. The factor analysis identified symptom domains similar to prior studies in other populations. These results show that individuals with the HD mutation are at increased risk to develop depressive symptoms at any time during the HD prodrome. The clinical presentation appears to be similar to other populations. Severity and progression are not related to the HD mutation.

Keywords

Huntington Disease; Depression; Suicide; Genetic testing

Introduction

Depression is a common mental disorder worldwide, ranking fourth in global burden among all illnesses (WHO 2012). It is often associated with other medical conditions, particularly neurodegenerative diseases (Lee et al. 2003; Costa et al. 2006; Rickards 2006; Raskind 2008). Huntington disease (HD) is an inherited neurodegenerative condition in which individuals carry an excessive number of cytosine-adenine-guanine (CAG) trinucleotide DNA repeats on chromosome 4. Affected individuals typically develop motor symptoms (chorea, bradykinesia, and dystonia) in adulthood, and also develop cognitive and psychiatric manifestations, including depression, with a progressive functional decline over two decades leading to premature death (Walker 2007; Ross et al. 2011). The psychiatric manifestations of HD, particularly depression, contribute to significant morbidity (Marder et al. 2000; Hamilton et al. 2003; Nehl et al. 2004; Beglinger et al. 2010) and early mortality due to suicide (Cummings 1995; Fiedorowicz et al. 2011).

In samples of individuals who were given a clinical diagnosis of HD based on motor symptoms, the prevalence of depressed mood has been reported in the range of 33% to 69% (Craufurd et al. 2001; Kulisevsky et al. 2001; Murgod et al. 2001; Paulsen et al. 2001; Leroi et al. 2002; Paulsen et al. 2005; van Duijn et al. 2007). Depression and other psychiatric manifestations have been reported at a higher frequency in those carrying the HD mutation during the prodromal period prior to motor symptom onset compared to samples negative for the HD mutation. Although some studies report up to 20% with clinically significant symptoms of depression at the time of evaluation (Julien et al. 2007; Kingma et al. 2008; van Duijn et al. 2008; Tabrizi et al. 2009), the magnitude and significance of this association with HD is variable. This variability may be due to small sample sizes, methodological differences in how depression is assessed, and the method of participant stratification based on prodromal or diagnosed disease status.

Structural and functional brain changes in the basal ganglia and cortex secondary to alterations in hormone and neurotransmitter levels underlie the pathophysiology of depression. Psychosocial factors specific to HD, including the stresses of a terminal illness and a decline in functioning also contribute to changes in the brain that result in depression. The mechanisms by which biological and social factors result in depression remain poorly understood. While standard treatments for depression are recommended for depressed HD gene carriers (Epping et al. 2011), empirical support is limited (Rosenblatt 2007; Phillips et al. 2008; Holl et al. 2010). Greater understanding of depression in this population promises to improve identification and treatment, and ultimately may reduce the prevalence of depression in gene carriers and its negative impact.

The Neurobiological Predictors of Huntington Disease Onset Study (PREDICT-HD) is the largest sample of individuals evaluated to date with prodromal HD (Paulsen et al. 2006; Paulsen et al. 2008). We have previously reported the presence of psychopathology, including depression, across several domains at the time of entry into this longitudinal study (Duff et al. 2007; Paulsen et al. 2008; Downing et al. 2011), and that depression is associated with worse cognitive performance (Smith et al. 2012). In this report we expand on these initial findings in a larger cohort, with over 800 prodromal HD individuals and over 200 participants who are gene-expansion negative from HD families. Our aim is to better characterize depression in a prodromal HD sample stratified by predicted time to motor diagnosis. Specifically, we examine the prevalence of depressive symptoms, severity, and associated clinical features in this sample and investigate the relationship between depression and time since genetic testing for the HD mutation. Additionally, we conduct a

factor analysis to identify core symptom domains in a subsample with clinically significant symptoms of depression.

Methods

Participants

Baseline visit data from 1026 participants were available. All participants had a positive family history of HD and had genetic testing prior to and independent of enrollment in PREDICT-HD, with 803 gene expansion positive (CAG repeats ≥ 36) participants and 223 gene expansion negative participants serving as healthy comparisons. All were 18 years of age or older and not diagnosed with manifest HD at study entry. Exclusion criteria included unstable medical or psychiatric illness, active substance abuse, history of a significant developmental cognitive disorder, significant history of head trauma or other CNS disease, the presence of a pacemaker or other metallic implants, use of antipsychotic medication in the 6 months before enrollment, or the use of phenothiazine antiemetic medication in the 3 months before enrollment. All participants provided informed consent as approved by their individual sites' Institutional Review Boards.

Procedures

At the baseline visit, participants provided a blood sample; underwent motor, cognitive, psychiatric, and functional assessments; and had a brain MRI scan. Information was obtained from participants regarding past medical and psychiatric histories, current medication use, and time since HD genetic testing. Motor exams were completed by certified motor raters using the Unified Huntington Disease Rating Scale (UHDRS) (HSG 1996) and all other assessments were obtained by trained research technicians.

The Beck Depression Inventory (BDI-II) is a 21-item self-rated scale that measures symptoms of depression (Beck et al. 1996): each question is scored on a scale of 0-3 corresponding to severity of the symptom during the prior two weeks. Total scores range from 0-63, with scores <13 defined as minimal depression, 14-19 defined as mild symptoms, 20-28 defined as moderate symptoms, and 29-63 defined as severe depression. The Beck Hopelessness Scale (BHS) is a 20-item self-report measure that assesses feelings of hopelessness over the previous week. A score >9 is associated with a high risk of suicide (Beck et al. 1990). The Symptom Checklist-90-Revised (SCL-90R) is a 90-item self-report scale of psychological symptomatology, with each item rated on a scale of 0 to 4 based on the degree of distress over the previous 7 days (Derogatis 1975). Global measures of psychiatric symptoms and scores for 9 specific symptom domains are produced from the scale. The raw scores are converted to *t*-scores normalized to a sample of non-psychiatric individuals by gender. Baseline results from all domains of the SCL-90R were previously reported from a smaller sample in PREDICT-HD (Duff et al. 2007). Results from the 13 items that comprise the depression subscale are used in this study. The UHDRS Behavioral scale has questions on severity and frequency of behavioral symptoms common to HD, measured on a 0-4 Likert Scale (HSG 1996). The Total Functional Capacity (TFC) is used in HD research to measure the ability to perform activities of daily living on a scale of 0-13, with higher scores indicating higher functioning (Shoulson et al. 1979).

Statistical Methods

Analyses were performed using SAS 9.2 (Cary, N.C., U.S.A.). Participants with the HD mutation were stratified into three groups based on their CAG-Age Product (CAP) score using methods developed for PREDICT-HD (Zhang et al. 2011). Briefly, the CAP score was derived from an accelerated failure-time model and is computed as $CAP = (\text{Age at entry}) \times (\text{CAG repeat length of HD mutant allele} - 33.66)$. CAP scores can be converted to a scaled

CAP score (CAP_S) based on a 5-year probability of diagnosis. Cutoffs for the three CAPs groups (low, medium, and high) were based on an optimization algorithm using PREDICT-HD participants. The low group comprised CAPs scores <0.67, the medium group CAP_S values were between 0.67 and 0.85, and the high group CAP_S scores were >0.85. Based on this stratification the estimated time to diagnosis for each CAP group was >12.8 years for the low group, between 12.8 and 7.6 for the medium group, and <7.6 years for the high group. Demographic measures across CAP groups were compared by analysis of variance. Categorical variables were compared using Chi-square tests. Differences in depression measures were analyzed across CAP groups and gene-negative participants using analysis of covariance (ANCOVA), with age, gender, and years of education as covariates. Individual CAP group comparisons were made using *t*-tests. The relationship between time since testing and BDI-II symptoms of depression was analyzed using multiple regression with age and gender as covariates and included an age by time since testing interaction term. UHDRS motor scores, TFC and CAG repeat lengths were analyzed across BDI-II severity groups by ANCOVA, with age, gender, and years of education as covariates.

Using the depression variables (21 BDI-II items, 13 SCL-90R items, 14 UHDRS items) as raw data, a factor analysis was conducted on the prodromal HD sample with BDI-II scores >13 (N=168) using principal component analysis as the method of extracting initial factors. Orthogonal factor rotation was then applied to facilitate the interpretation of extracted factors. The number of factors was determined based on both the magnitude of eigenvalues and the scree plot. A variable was retained for a factor if its loading was larger than 0.4.

Results

Demographics and Measures of Depression by CAP Groups

Demographic data are presented in Table 1. BDI-II scores (unadjusted) dichotomized between no or minimal symptoms (<13) vs. mild or more severe symptoms (>13) are presented in Figure 1A. A BDI-II score >13 is considered clinically significant (Beck et al. 1996). HD gene expansion negative participants were compared to expansion positive prodromal individuals stratified into three groups according to their CAP Score. A significantly higher proportion of gene-expanded individuals as a whole ($\chi^2=30.7, p<0.001$) and in each CAP group have BDI-II scores >13 compared to the expansion negative group. When comparing the CAP groups to each other, there was no significant difference in the proportion with BDI-II>13 ($\chi^2=3.35, p=0.187$). The percentage of individuals in the expansion-negative and CAP groups with mild, moderate, or severe BDI-II symptoms are presented in Figure 1B. While the vast majority in all groups had minimal depressive symptoms, a higher percentage of participants in the CAG expansion-positive groups had more severe symptoms. When comparing BDI-II severity groups in each CAP group versus controls, all CAP groups had significantly more individuals in the mild BDI-II category, but only the medium CAP group had significantly larger proportions of individuals in each BDI-II severity group compared to controls. Similar to the BDI-II, a higher proportion of HD gene positive individuals reported more frequent depressive symptoms on the UHDRS behavioral assessment compared to the expansion negative group (data not shown).

The ANCOVA results for BDI-II ($F(3,1017)=13.25, p<0.0001$), BHS ($F(3,999)=13.73, p<0.0001$), and SCL-90R depression ($F(3,1015)=6.63, p=0.0002$) scores across CAP groups are presented in Table 2. Whereas mean BDI-II scores for all CAP groups were in the minimal symptom range, symptom levels were significantly higher for each CAP group compared to the expansion-negative comparison group (low CAP vs. expansion-negative control $t(428)=2.69, p=0.007$, medium CAP vs. control: $t(504)=6.1, p<0.0001$, high CAP vs. control $t(532)=4.5, p<0.0001$). Among the CAP groups, the only significant difference in BDI-II scores were between the low and medium groups ($t(488)=2.97, p=0.003$). ANCOVA

results for the mean number of BHS items by CAP group showed low levels of hopelessness; however, the results are higher for the gene-positive CAP groups. SCL-90R depression measures were slightly higher among gene-positive individuals, and the medium CAP group was found to have the highest mean level of symptoms, although there were no significant differences between CAP groups.

Characterization of Depression in Prodromal HD Based on Symptom Severity

Results for differences among prodromal HD severity groups (Minimal, Mild, Moderate, Severe) are shown in Table 3 and discussed below. A higher proportion of females had mild, moderate, or severe depressive symptoms compared to the total sample. The group with severe depressive symptoms also was more likely to self-report a past history of depression that required treatment (93%). A history of depression was also significantly higher in the gene-positive group. The proportion of individuals in each group taking an antidepressant at baseline also increased with greater depression severity, with the highest percentage in the severe depression group. ANCOVA of motor scores showed that total motor score was low across all BDI-II groups, but was slightly higher with more severe depressive symptoms. Total functional capacity also decreased with increasing depressive symptoms, although the decrease in TFC was only one point between the minimal and severe BDI-II groups. CAG length was not statistically different across BDI-II groups.

The effects of age and time since testing on severity of symptoms of depression from the BDI-II were analyzed by ANCOVA, with gender and education level as covariates. An age by time-since-testing interaction term was included in the model. In this model, age and time since testing were negatively related to depressive symptoms, but only the age term was statistically significant ($F(1,762)=6.12, p=0.013$).

Factor Analysis of Depressive Symptoms in Prodromal HD

A factor analysis was conducted using BDI-II, SCL-90R depression subscale, and UHDRS behavioral scale questions from the 168 prodromal HD participants who endorsed mild or greater symptoms of depression on the BDI-II, and had data from the other assessments were used. Analysis of the eigenvalues and scree plot of eigenvalues suggested retention of eight factors, which accounted for 58.1% of the total variance, and each factor was given a descriptive term based on the predominant questions associated with the factor. The results of the factor analysis and factor descriptions are shown in Table 4.

Discussion

These findings from PREDICT-HD provide the most comprehensive report to date on depressive symptomatology in prodromal HD. Our analysis is the strongest confirmation that while clinically significant depression occurs in only a fraction of individuals in the HD prodrome, it can occur at any time and is not related to CAG length or time since genetic testing. This study also provides important data on treatment trends, demographic and symptomatic features of depression in prodromal HD mutation carriers, and advances our understanding of this disabling condition.

We expand here on our previous findings (Paulsen et al. 2006; Duff et al. 2007; Downing et al. 2011) using a larger PREDICT-HD sample, an updated stratification methodology, and additional assessments. Our results consistently show a higher prevalence of depression in mutation positive individuals, although the overall group means remain in the minimal symptom range. Prior studies of prodromal depression with smaller samples (Julien et al. 2007; van Duijn et al. 2008; Tabrizi et al. 2009) also found increased prevalence of depression; however, only one study (Julien et al. 2007) reported a statistically significant

difference compared to study controls, and this was only within one year prior to diagnosis. We have also reported that suicide risk increases in individuals who are closer to motor diagnosis (Paulsen et al. 2005). Studies from our group and others (Craufurd et al. 2001; Kulisevsky et al. 2001; Murgod et al. 2001; Leroi et al. 2002; Paulsen et al. 2005) show the increase in depressive symptoms continues after diagnosis, peaking in the early stages of diagnosed illness (Paulsen et al. 2005). Akin to the report of Downing et al., here using the updated CAP score, the highest mean level of depressive symptoms is in the medium CAP group. This finding has been reported for other behavioral symptoms in PREDICT-HD (Beglinger et al. 2008; Duff et al. 2010). One explanation for these findings may be that individuals have decreased insight or awareness of symptoms as they approach diagnosis, thus they report fewer symptoms than may actually be present (Paulsen et al. 2006). The finding from Julien et al. of increased depressive symptoms and from Paulsen et al. showing increased suicide risk before a diagnosis of HD may appear on the surface to be inconsistent with the peak of depressive symptoms in the medium CAP group here; however, there are two important differences to note. First, the stratification methods used are completely different between studies, making direct comparisons difficult: for example, the high CAP group here includes a longer span of years before diagnosis (up to 7.6). Julien et al. have follow-up data on their participants, including the time of diagnosis, while our results here are only based on estimated proximity to diagnosis. It is not possible to accurately estimate proximity to diagnosis within one year. In Paulsen et al. disease status is only stratified by neurological symptoms. Second, the studies have different assessments of depression, with Julien et al. using a structured clinical assessment rather than the self-reporting of symptoms used here. Future studies of longitudinal PREDICT-HD data will provide additional insight into depressive symptoms and illness progression.

As noted above, one caveat to comparing the prevalence of depression across studies is that they all differ in the assessments used to evaluate depression and also in criteria for defining individuals with prodromal HD. In this study, all expansion-positive individuals have not yet been given the traditional diagnosis of manifest HD. This is also observed here in comparing BDI-II scores with the SCL-90R depression subscale, for which mean scores in each CAP group were all higher than gene-negatives, but none are significantly different from each other. This may indicate that the BDI-II is more sensitive to differences in depressive symptoms between CAP groups. It is also possible that the slight decrease in symptoms in the high CAP group on the BDI-II is related to decreased insight. Based on the present analysis of baseline data, there does not appear to be a consistent relationship between depressive symptoms and predicted proximity to diagnosis.

Variables traditionally associated with depression severity are also present in our prodromal HD sample. An increased frequency of depression in females is consistent with prior studies of the epidemiology of depressive disorders (Coryell et al. 1992). A linear trend was observed between past history of depression and the BDI-II severity groups, and we found a higher lifetime history of depression requiring treatment than previous studies in prodromal HD. The 39% observed here is also higher than lifetime history of depression reported in the general population (Kessler et al. 2003). In our sample we previously reported a linear trend between antidepressant use and depression severity (Rowe et al. 2011), but we show here that a significant proportion of individuals were not taking medication despite having significant symptoms of depression. We have also reported that depression in this sample contributes to cognitive impairment (Smith et al. 2012) and that depressive symptoms are correlated with levels of perceived stress and number of negative life experiences (Downing et al. 2011).

Previous studies have examined the relationship between depression and genetic testing due to early concerns about the possibly negative psychological effects of a positive test result;

the results of these studies vary as to the likelihood of depression developing after testing (Codori et al. 1994; Lawson et al. 1996; Almqvist et al. 2003; Decruyenaere et al. 2003; Lickleder et al. 2008). We noted in Downing et al. a complex relationship between age, time since genetic testing and perceived stress: individuals under 34 had increased stress with longer time since testing, but those over 34 noted decreased stress with increased time after testing. In our analysis here on the relationship between depression, age, and time since testing, we only identified a significant relationship between age and depression, with older age at the time of genetic testing associated with fewer symptoms of depression. Our results suggest that genetic testing does not strongly contribute to depression over time after testing. With older age, individuals in the prodromal HD stage may be less susceptible to depression, possibly due to more developed coping mechanisms in response to life events.

The lack of association with CAG length and depression severity is consistent with prior studies (Weigell-Weber et al. 1996; Berrios et al. 2001). Motor symptom and depression severity are unrelated to each other in diagnosed HD (Zappacosta et al. 1996; Thompson et al. 2002), and although we observed a slight increase in motor scores with depression severity, the difference was not clinically significant. The decrease in TFC associated with increasing depression severity was significantly related; however the decrease was only one point, which does not indicate a large decline in functional capacity. There may be aspects of daily functioning affected by depression not measured by the TFC.

The factor structure of psychiatric symptoms across all domains have been reported in HD (Marder et al. 2000; Craufurd et al. 2001; Kingma et al. 2008; Rickards et al. 2011); our factor analysis in participants with at least mild symptoms is the first focusing exclusively on depressive symptoms in HD. Only a few questions were inconsistent with others in the eight factors, particularly questions regarding anxiety, which were present in 3 different factors. Although there is evidence that apathy is a distinct syndrome in HD that correlates with disease progression (Levy et al. 1998; Naarding et al. 2009; van Duijn et al. 2010), we included UHDRS questions regarding apathy in the factor analysis and found that they loaded onto the same factor as depressed mood. Factor models of the BDI-II have been proposed, often dividing the scale into somatic or cognitive (negative thoughts about oneself) domains as primary factors, with affective symptoms loading onto one or the other (Ward 2006; Chilcot et al. 2011). A more recent analysis determined that the best model for the BDI-II was a general factor model encompassing all BDI-II questions (Ward 2006). Our analysis, using data from other scales of depression overall support a model with a cognitive factor, a somatic factor, and additional factors comprising common symptoms of depression. Two of the prominent symptom domains included physical symptoms and activating symptoms, including irritability and aggression. These symptoms can occur with depressed mood, but also separately. Irritability is a common behavioral manifestation in HD (Craufurd et al. 2001). Here we have chosen to focus our initial analysis using complete scales of depressive symptoms, but the factor analysis provides an initial step for future studies to address the intersection of depression with other manifestations of HD.

One limitation in the interpretation of these results is how closely the PREDICT-HD sample represents the entire population of individuals with prodromal HD. Recent studies have estimated approximately 15% of those at risk for HD obtain genetic testing (Tassicker et al. 2009; Morrison et al. 2011), indicating that our study sample is drawn from a minority of those carrying the HD mutation. Prior research also indicates that those who obtain genetic testing may be more likely to have a psychological profile that is better able to cope with a positive gene test result (Codori et al. 1994). If this is true, our sample might actually underestimate the true prevalence of depression among prodromal HD individuals.

As PREDICT-HD is a naturalistic study, the uncontrolled use of medications or other therapies confounds the report of symptoms. Although we have ascertained the proportion of individuals taking antidepressants at the time of study entry, we do not have information about how long they had symptoms of depression prior to treatment, or how those symptoms have changed with treatment. Antidepressant use may be for reasons other than depression, such as irritability, smoking cessation, or insomnia. Based on these data we do know that only a proportion of individuals with significant depressive symptoms were taking medication at the time of baseline assessments, making it likely that many individuals are not being adequately treated for depression.

One question is whether the HD mutation itself contributes to increased risk of depression. Imaging studies have identified functional brain changes specific to individuals with HD and depression, supporting the importance of biological factors (Mayberg et al. 1992; Paradiso et al. 2008; Unschuld et al. 2012). Current evidence supports a model in which biological risk factors interacting with life stresses/events lead to the development of depression. From these results, the presentation of depressive symptoms in the HD prodrome appears to be similar to non-HD populations, and it can occur years before diagnosis. Further studies from this population will not only improve diagnosis and treatment of depression in HD, but also for all persons affected by this debilitating condition.

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Figure 1A.

BDI-II Depression Severity (BDI-II > 13 indicating clinically significant symptoms) in HD CAG-Expansion Negatives and HD CAG-Expanded Individuals by CAG-Age Product (CAP) Group. Chi-square statistic for BDI > 13 between all expansion positive versus expansion negative = 30.7, $p < 0.001$.

Figure 1B.

BDI-II Severity (mild, moderate, or severe) in CAG-Expansion Negatives and CAG-Expanded Individuals by CAG-Age Product (CAP) Group. The percentages within each CAP group and the expansion negative group add up to the percent with BDI-II > 13 in Figure 1A (white bars).

Table 1

Demographics by CAG-Age Product (CAP) Score Group

		Expansion-Positive CAP Score Group		
	Expansion-Negative	Low	Medium	High
Number	223	207	284	312
Gender F/M (%/%)	143/80 (64%/36%)	140/67 (68%/32%)	186/98 (65%/35%)	186/126 (60%/40%)
Age ¹ Mean years (SD)	43.7 (11.6)	35.0 (7.6)	41.1 (9.4)	44.1 (9.8)
Education Level Mean years (SD)	14.7 (2.6)	14.5 (2.5)	14.4 (2.7)	14.2 (2.8)
CAG Repeats ² Mean (SD)	20 (3.5)	40.9 (1.6)	42.2 (2.1)	43.8 (2.8)
Time since genetic testing ³ Mean years (SD)	4.66 (4.65)	3.13 (3.78)	3.78 (3.30)	4.66 (4.24)

Group differences non-significant unless noted.

¹ ANOVA $F(3,1022)=42.26, p<0.0001$ ² ANOVA for Low/Medium/High CAP groups: $F(2, 800)=108.82, p<0.0001$ ³ ANOVA $F(3,1022)=8.28, p<0.001$

Table 2

ANCOVA Results (Adjusted Means and 95% confidence intervals) for Beck Depression Inventory- II (BDI-II), Beck Hopelessness Scale (BHS), and Symptom Checklist-90 Revised (SCL-90R) Depression Measures by CAP Group

Independent Variable	Expansion-Positive CAP Score Group				
	Expansion-Negative	Low	Medium	High	Group Comparisons⁴
BDI-II ¹	4.7 (3.6-5.7)	6.8 (5.7-8.0)	9.1 (8.1-10.0)	7.9 (6.9-8.8)	C < L < M; C < H
BHS ²	2.5 (2.0-3.0)	3.3 (2.7-3.9)	4.6 (4.1-5.1)	4.1 (3.6-4.5)	C < L < M ~ H
SCL-90R Depression ³	49.9 (48.1-51.7)	53.2 (51.3-55.2)	55.2 (53.6-56.8)	53.7 (52.2-55.3)	C < L ~ M ~ H

¹ ANCOVA Covariates: age, gender, years of education. ANCOVA $F(3,1017)=13.25$, $p<0.0001$ for the omnibus CAP group test.

² ANCOVA Covariates: age, gender, years of education. ANCOVA $F(3,999)=13.73$, $p<0.0001$ for the omnibus CAP group test.

³ ANCOVA Covariates: age, years of education. SCL-90R results are t-scores standardized to a population of individuals without psychiatric symptoms by gender. ANCOVA $F(3,1015)=6.63$, $p=0.0002$ for the omnibus CAP group test.

⁴ C = Expansion Negative (Control), L = Low CAP group, M = Medium CAP group, H = High CAP group. The < sign indicates a significant difference ($p < 0.05$) between groups, and the ~ sign indicates nonsignificant group difference.

Table 3

Measures of Clinical Variables By Depression Severity in Prodromal HD

	BDI-II Symptom Level			
	Minimal	Mild	Moderate	Severe
Female Gender ¹ (%)	377/625 (60%)	71/89 (80%)	43/62 (69%)	21/27 (78%)
History of Depression ² (%)	189/625 (30%)	54/89 (61%)	45/62 (73%)	25/27 (93%)
Current Antidepressant Use (%) ³	103/506 (17%)	31/86 (36%)	23/60 (38%)	12/27 (56%)
Motor Score Mean (SD) ⁴	4.1 (4.8)	5.2 (4.8)	6.8 (6.4)	6.7 (3.7)
TFC Mean (range) ⁵	12.9 (9-13)	12.8 (9-13)	12.4 (7-13)	12.0 (7-13)
CAG Length Mean (range) ⁶	42.3 (38-61)	42.7 (39-47)	43.2 (38-51)	43.2 (39-48)

¹Gender for total prodromal HD sample: 64% F, 36% M, $\chi^2(3) = 16.22, p = 0.001$

Proportion of total in each BDI group, $\chi^2(3) = 99.74, p < 0.0001$

²History of depression by gene status ($\chi^2(1) = 16.56, p < 0.0001$):

Gene-positive: 313/803 (39%)

Gene-negative: 54/223 (24%)

³ $\chi^2(3) = 46.12, p < 0.0001$

⁴ $F(3, 793) = 5.34, p < 0.0001$ for the omnibus BDI-II group test by ANCOVA. Covariates for all ANCOVAs included age, gender, years of education.

⁵ $F(3, 790) = 33.53, p < 0.0001$ for the omnibus BDI-II group test by ANCOVA

⁶ $F(3, 794) = 0.63, p = 0.59$ for the omnibus BDI-II group test by ANCOVA

Table 4

Factor Analysis Results from BDI-II, SCL-90R Depression, and UHDRS Behavioral questions for prodromal HD subjects with at least mild symptoms of depression (n = 168). Only factor loading values > 0.4 were retained.

	Factors and loading values*							
	1	2	3	4	5	6	7	8
BDI 2-Pessimism							0.61	
BDI 3-Past Failure	0.57							
BDI 4-Loss of Pleasure							0.59	
BDI 5-Guilty Feelings	0.63							
BDI 7-Self Dislike	0.55							
BDI 8-Self Criticalness	0.50							
BDI 9-Suicidal Thoughts					0.73			
BDI 11-Agitation				0.45				
BDI 12-Loss of Interest							0.61	
BDI 13-Indecisiveness							0.41	
BDI 14-Worthlessness	0.64							
BDI 15-Loss of Energy		0.74						
BDI 16-Changes in Sleep		0.50						
BDI 18-Changes in Appetite				0.56				
BDI 19- Poor Concentration		0.41						
BDI 17-Irritability		0.59						
BDI 20-Tiredness/Fatigue		0.78						
BDI 21-Loss of Interest in Sex								0.81
UHDRS 25a-Depressed Mood (Frequency)						0.73		
UHDRS 25b-Depressed Mood (Severity)						0.78		
UHDRS 26a- Apathy (Frequency)						0.53		
UHDRS 26b- Apathy (Severity)						0.61		
UHDRS 27a- Low Self-Esteem/Guilt (Frequency)	0.69							

	Factors and loading values*							
	1	2	3	4	5	6	7	8
UHDRS 27b- Low Self-Esteem/Guilt (Severity)	0.68					0.42		
UHDRS 28a- Suicidal Thoughts (Frequency)					0.83			
UHDRS 28b- Suicidal Thoughts (Severity)					0.80			
UHDRS 29a- Anxiety (Frequency)				0.44				
UHDRS 29b- Anxiety (Severity)				0.53		0.44		
UHDRS 30a- Irritable Behavior (Frequency)				0.75				
UHDRS 30b- Irritable Behavior (Severity)				0.73				
UHDRS 31a- Disruptive/Aggressive Behavior (Frequency)				0.78				
UHDRS 31b- Disruptive/Aggressive Behavior (Frequency)				0.75				
SCL 5- Loss of sexual interest/pleasure								0.84
SCL 14- Feeling low in energy/slowed down		0.75						
SCL 15- Thoughts of ending life					0.75			
SCL 20- Crying easily			0.65					
SCL 22- Feeling trapped/caught			0.54					
SCL 26- Blaming self for things	0.49		0.56					
SCL 29- Feeling lonely			0.69					
SCL 30- Feeling blue			0.69					
SCL 31- Worrying too much about things			0.72					
SCL 32- Feeling no interest in things		0.49					0.46	
SCL 54- Feeling hopeless about future					0.42			
SCL 71- Feeling everything is an effort		0.47						
SCL 79- Feeling of worthlessness	0.49		0.45					

Table 4 Caption:

* Factor descriptive terms based on the predominant questions associated with the factor:

1) low self-esteem

- 2)predominantly physical symptoms
- 3)isolation and sadness
- 4)activation symptoms, including irritability/agitation
- 5)suicidal thoughts
- 6)low mood/apathy
- 7)loss of interest
- 8)low sexual interest