Executive impairment is associated with unawareness of neuropsychiatric symptoms in premanifest and early Huntington's disease

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ABSTRACT

Objective: Unawareness of neuropsychiatric symptoms appears to be common in Huntington's disease (HD), but the clinical correlates of unawareness are unclear. Identifying predictors of unawareness is important for improving diagnosis of neuropsychiatric symptoms, and cognitive impairment, specifically executive impairment, may be a potential important predictor of unawareness. The authors examined whether unawareness of neuropsychiatric symptoms is more common in early HD compared to premanifest HD, and whether executive task performance was associated with awareness, independent of demographic, motor or mood variables.

Method: 132 gene-positive participants (60 premanifest and 72 early diagnosed) from the multicentre TRACK-HD study were included. Participants and their informants completed self- and informant-versions of the Frontal Systems Behavior Scale, which measures executive dysfunction, apathy, and disinhibition symptoms. Awareness was measured as the discrepancy between self- and informant-reports across premanifest and early HD groups. Participants' executive task performance was then assessed as a predictor of unawareness across the whole group.

Results: Premanifest participants reported *higher* levels of executive dysfunction, apathy and disinhibition than their informants, whereas early HD participants reported *less* executive dysfunction and apathy than their informants, indicating that unawareness is more common after diagnosis. Impaired executive task performance was related to unawareness of executive dysfunction and apathy, independent of demographic, motor and mood variables.

Conclusions: Executive impairment is a useful early predictor of unawareness of neuropsychiatric symptoms in HD. Clinicians should closely monitor HD patients with executive impairment for unawareness, and consider this when assessing neuropsychiatric symptoms in HD and providing education to patients and families.

Keywords: Huntington's disease; apathy; cognition; behaviour; awareness

Public Significance Statement: The present study suggests that individuals with pre-symptomatic and early Huntington's disease who show cognitive impairment, specifically executive dysfunction, are more likely to be unaware of their own neuropsychiatric symptoms. Therefore clinicians should consider a patient's cognitive difficulties when both assessing neuropsychiatric symptoms, and providing education to the patient and their family.

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease characterised by motor, cognitive and neuropsychiatric symptoms (Walker, 2007). Among the neuropsychiatric manifestations of HD, apathy, executive dysfunction and disinhibition are often evident prior to clinical diagnosis (Duff et al., 2010; Hamilton et al., 2003; Martinez-Horta et al., 2016), are a source of distress to families and carers, and are associated with functional decline (Fisher, Andrews, Churchyard, & Mathers, 2012; Hamilton et al., 2003; Nance & Sanders, 1996). One of the challenges for the accurate assessment of neuropsychiatric symptoms in HD is patients' unawareness of their own symptoms. Deficits in awareness of at least some types of neuropsychiatric symptoms are common in HD (Sitek, Thompson, Craufurd, & Snowden, 2014). Early identification of unawareness is essential for improving the diagnosis of neuropsychiatric symptoms, as well as targeting education for family members regarding unawareness. Unawareness of neuropsychiatric symptoms in HD has been correlated with motor symptom severity, as a marker of disease severity; however, cognitive impairment, specifically executive impairment, has also been identified as a potential important correlate of unawareness. Given executive impairment often occurs prior to motor onset, it may be a more useful predictor of awareness of neuropsychiatric symptoms than motor severity.

An association between cognition and unawareness of neuropsychiatric symptoms in HD has been shown in several previous studies. For example, Chatterjee and colleagues reported that unawareness of neuropsychiatric symptoms in manifest HD was associated with poorer cognition (Chatterjee, Anderson, Moskowitz, Hauser, & Marder, 2005). Another study using a mixed premanifest and manifest HD sample, reported that performance on executive function measures, but not on a more general cognitive task, was correlated with unawareness of apathy (Mason & Barker, 2015). In this latter study, unawareness of apathy also correlated with severity of motor symptoms, and so it not clear whether the relationship between

executive dysfunction and unawareness was independent of motor symptoms. Given that both unawareness and executive dysfunction can occur in HD prior to the manifestation of motor symptoms, a relationship between executive dysfunction and unawareness of neuropsychiatric symptoms might be present across both premanifest and manifest gene-positive individuals.

Unawareness of neuropsychiatric symptoms in HD is typically measured using either by self-report, informant-report, or clinician-rated scales (Malloy & Grace, 2005). For some scales, both self-report and informant-report versions are available, and the discrepancy between these ratings is often used as an index of awareness (Chatterjee et al., 2005; Duff et al., 2010; Ho, Robbins, & Barker, 2006; Hoth et al., 2007). That is, for a given rating scale, a patient report endorsing fewer or less severe symptoms compared to their informant is commonly interpreted as evidence of unawareness. This approach has limitations due to the subjective nature of both self- and informant-ratings, but informants generally have the best knowledge of the patient in their home environment, and therefore it remains the most commonly used way to assess awareness in HD (Sitek et al., 2014). In diagnosed HD, patients under-report symptoms of apathy and executive dysfunction compared to their informants, indicating unawareness of these symptoms (Chatterjee et al., 2005; Ho et al., 2006; Hoth et al., 2007). In one study that included *only premanifest HD*, participants who were estimated to be far from disease onset reported more symptoms of executive dysfunction, apathy and disinhibition on a shortened version of the Fronal Systems Behavior Scale (FrSBe) than their informants, whereas those estimated to be close to onset reported fewer symptoms than their informants (Duff et al., 2010), indicating that the manifestation of unawareness depends on disease progression. Although this was an important finding, the authors used a shortened 24-item version of the FrSBe that is not widely available, and it is unclear if the full version of the FrSBe would yield these same results. This same pattern of

results reported in Duff et al. has also been found with awareness of other types of neuropsychiatric symptoms (Epping et al., 2016). Another recent study found no significant differences between self and informant apathy ratings in a *mixed premanifest and manifest sample*, however, in this study premanifest and manifest groups were not analysed separately (Mason & Barker, 2015). Given there may be differences in awareness between premanifest and manifest HD, unawareness should be characterised separately for premanifest and manifest HD.

The aims of this study were a) to determine if unawareness of neuropsychiatric symptoms was more common in manifest HD compared to premanifest HD, and b) to assess to what extent unawareness of neuropsychiatric symptoms relates to executive impairment, independent of motor progression, across the whole premanifest and manifest HD sample. In order to achieve these aims, we first compared premanifest HD and early manifest HD groups on discrepancies between self- and informant-ratings of neuropsychiatric symptoms of executive dysfunction, apathy and disinhibition using the full 46-item version of the Frontal Systems Behavior Scale (FrSBe). We hypothesised that premanifest participants would report more executive dysfunction, apathy and disinhibition than informants, but that for early HD group, participants would report less severe symptoms than informants, indicating lower self-awareness in this group. We then assessed whether an estimate of executive impairment, i.e., a composite of several executive tasks, was a significant predictor of self-informant discrepancies on the FrSBe subscales, after controlling for demographic features, self-ratings of depression and anxiety, and motor symptom severity (as a proxy for general disease progression). We hypothesised that the executive composite would predict discrepancies on all FrSBe subscales, independent of motor or mood symptoms, with poorer performance on the executive tasks associated with unawareness of executive dysfunction, apathy and disinhibition symptoms.

Method

Participants

Participants were 132 individuals with premanifest or early HD who took part in the baseline assessment of the multidisciplinary, multi-site (Paris, Leiden, Vancouver and London), longitudinal TRACK-HD study (Tabrizi et al., 2009). For inclusion in the study, participants' records were required to have both self-report and informant ratings of neuropsychiatric symptoms, as well as motor, mood and cognitive task performance data. Participants were between 18 and 65 years of age and had no history of major neurological illness (except HD), major psychiatric disorder or significant head injury. The premanifest HD group constituted individuals with genetically-confirmed huntingtin gene-expansion (≥39 CAG repeats) together with never having received a clinical diagnosis of HD, a Total Motor Score ≤ 5 on the Unified Huntington's Disease Rating Scale (UHDRS)(Huntington Study Group, 1996) and Disease Burden Score ≥ 250 (calculated as age x [CAG-35.5]) (Penney, Vonsattel, MacDonald, Gusella, & Myers, 1997). The early HD group comprised people at Stage 1 or 2, as indicated by the UHDRS Total Functional Capacity score (Shoulson & Fahn, 1979), which includes individuals who range from minimal clinical impairment to moderate clinical impairment. In addition to the premanifest and early HD participants, whose results are reported in the paper, we used the 119 Track-HD healthy controls (who have no informant ratings) as a study-specific comparison sample to indicate how the HD groups differed from controls on the FrSBe (see Table 1). Healthy controls were either: spouses or partners of clinical participants with premanifest or early HD who had no family history of HD; or, siblings confirmed to be gene-negative.

INSERT TABLE 1 HERE

Demographic and clinical data are shown in Table 1. All groups had similar gender ratios and education levels. The early HD group was older than the premanifest HD group, as is typically observed given the progressive nature of HD.

To determine the generalisability of our sample, which included only HD participants with informants, we compared their demographic and clinical characteristics to the remaining Track-HD participants who had no informant reports, and were therefore ineligible for the current study. We found no significant differences in ages, education levels, CAG repeat lengths, disease burden scores, Total Motor Scores, Total Functional Capacity, or self-reported anxiety or depression (all *ps* > .13). With respect to gender, however, in the early HD group only, participants with an informant were more likely to be men than those without informants ($p = .005$).

Materials

Frontal Systems Behavior Scale (FrSBe)

The FrSBe (Grace & Malloy, 2001) is a 46-item rating scale that assesses behaviours that are clinically and theoretically linked to frontal lobe dysfunction. The rating scale comprises three subscales: Apathy, Disinhibition, and Executive Dysfunction. The FrSBe has good psychometric properties and validity to assess neuropsychiatric symptoms in HD (Julie. C. Stout, Ready, Grace, Malloy, & Paulsen, 2003). Higher scores on the FrSBe indicate more frequent neuropsychiatric symptoms. Although not our primary outcome measures, we compared the group ratings on the FrSBe subscales, and confirmed they showed the expected pattern (Table 1). Specifically, the early HD group self-reported more frequent symptoms than healthy controls on all subscales (Executive Dysfunction: $p < .001$, $d = .83$; Apathy $p < .001$, $d = .71$; Disinhibition: $p = .01$, $d = .35$), and more than the premanifest group for two

of the three subscales (Executive Dysfunction: $p = .01$, $d = .25$; Apathy: $p = .002$, $d = .27$). For informant reports, the early HD group was rated as having more frequent symptoms than the premanifest group on all subscales (Executive Dysfunction: $p < .001$, $d = .99$; Apathy: $p < .001$, $d = .84$; Disinhibition: $p < .001$, $d = .63$).

We used discrepancies between self- and informant-reports on the FrSBe(Grace & Malloy, 2001) as an indicator of awareness of neuropsychiatric signs. For each participant, we calculated discrepancies between self-reports and informant-reports by subtracting the informant-report from the self-report for each subscale score. Positive scores indicated that the participant reported more frequent neuropsychiatric symptoms than their informant, whereas a negative score indicated that the participant reported less frequent symptoms than their informant.

Executive Function Composite

We created a composite of executive function tasks using attention, set-shifting and working memory tasks from the cognitive battery used in TRACK-HD (Julie C. Stout et al., 2012). This composite was comprised of Trail Making Test (TMT) A and B time to completion, Symbol Digit Modalities Test (number of items correct), and the Spot the Change visual working memory test – Set Size 5 score (number correct adjusted for guessing). For each participant, we standardised task scores separately for each test using the healthy control group as the population, and averaged these four standardized scores to obtain the Executive Composite score. Higher scores on the composite indicate better performance.

Motor and Mood Measures

We estimated motor signs using the UHDRS Total Motor Score as a proxy for general disease progression. We assessed symptoms of depression and anxiety using the Hospital

Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). Scores of eight or higher on either anxiety or depression scales indicate a possible mood disorder. Premanifest and early HD groups were not significantly different on self-reported anxiety or depression.

Statistical Analyses

To determine if unawareness of neuropsychiatric symptoms is more common in early HD compared to premanifest HD, we used the scores for each of the three FrSBe subscale scores (Executive Dysfunction; Apathy; or Disinhibition) as the dependent variable in three mixed between-within ANOVAs. The rater (self or informant) was the within-subjects variable, and the group (premanifest or early HD) was the between-subjects variable. We adjusted for multiple planned comparisons using Bonferroni correction, and calculated effect sizes using partial eta squared. Next, to assess whether awareness of neuropsychiatric symptoms was related to cognitive impairment, independent of general disease progression and mood symptoms, we used a series of three linear multiple regressions using the discrepancy scores from the FrSBe as the dependent variables, and the Executive Function Composite as the independent variable. To control for demographic variables (age, gender, site and education), general disease progression (UHDRS Total Motor Score) and self-reported mood symptoms (HADS Anxiety and Depression scores), we entered these variables at Step 1. We then entered the Executive Function Composite at Step 2, and examined whether it emerged as a significant predictor of discrepancy on the relevant FrSBe subscale.

Results

Comparisons between premanifest and early HD groups on self- and informant-ratings on FrSBe subscales

For the Executive Dysfunction subscale, both participants and their informants rated executive dysfunction higher in the early HD group compared to the premanifest group (main effect of group: F (1, 129) = 16.75, p <.001, η^2_p = .12 [large effect size]). A significant rater x group interaction effect in this ANOVA indicated that whereas premanifest participants reported *more* executive dysfunction symptoms compared to their informants, early HD participants reported *less* executive dysfunction compared to their informants (see Figure 1a; F (1, 129) = 17.54, p < .001, η^2_p = .12 [large effect size]). The main effect of rater was not significant (F (1, 129) = 1.90, p = .17, η^2_p = .02).

For the Apathy subscale, early HD participants and their informants reported higher levels of apathy than premanifest participants and their informants, reflected by a significant main effect of group (F (1, 129) = 11.25, p = .001, $\eta^2_{partial}$ = .08 [medium effect size]). The discrepancy between self- and informant-ratings also differed across the early HD and premanifest groups, reflected by a significant rater x group interaction (F (1, 129) = 12.41, p = .001, $\eta^2_{partial}$ = .09 [medium effect size]). Again, premanifest participants reported *more* apathy compared to their informants, whereas early HD participants reported *less* apathy compared to their informants (see Figure 1b). The main effect of rater was not significant (F (1, 129) = .54, p = .47, $\eta^2_{partial}$ = .004).

Similar to the other FrSBe subscales, there was a significant main effect of group for the Disinhibition subscale: early HD participants and their informants reported higher levels of disinhibition than premanifest participants and their informants (F (1, 129) = 7.56, p = .007, $\eta^2_{partial}$ = .06, [medium effect size]). We also found a significant rater x group interaction that indicated that whereas premanifest participants reported *more* disinhibited behaviour compared to their informants, early HD participants reported similar levels of disinhibition compared to their informants (F (1, 129) = 8.52, p = .004, $\eta^2_{partial}$ = .06 [medium

effect size]; see Figure 1c). Finally, there was again no significant main effect of rater (F (1, 129) = 3.46, p = .07, $\eta^2_{partial}$ = .03).

INSERT FIGURE 1 HERE

Relationship between performance on Executive Composite and Self-Informant Discrepancies on FrSBe subscales

For the patient-informant discrepancies in the *Executive Dysfunction* subscale of the FrSBe, only the Executive Composite score was a significant predictor; that is, in the multiple regression model, in which we entered all other predictors in Step 1 (demographic variables, UHDRS motor score, and HADS scores), and Executive Composite in Step 2, only the Executive Composite was associated with the discrepancy (β = -.39, t = -2.65, p = .009). Specifically, poorer executive task performance was associated with a tendency to patient under-reporting Executive Dysfunction symptoms on the FrSBe, in comparison to their informants (see Figure 2). The final model accounted for 21% of the variance associated with self-informant discrepancies, F (10, 129) = 3.11, p = .001.

For the patient-informant discrepancies in the *Apathy* subscale of the FrSBe, the Executive Composite score was a significant (but not the only) predictor; that is, in the multiple regression model, in which we entered all other predictors in Step 1 (demographic variables, UHDRS motor score, and HADS scores), and Executive Composite in Step 2, both the Executive Composite and HADS Depression were associated with the discrepancy. That is, participants whose scores were worse on the Executive Composite tasks tended to under-report Apathy symptoms on the FrSBe in comparison to their informants (β = -.44, t = -3.06, p = .003). Participants who reported more depression symptoms tended to endorse higher

Apathy levels on the FrSBe compared to their informants, β = -.25, t = -2.36, p = .02. Overall the regression model was significant and accounted for 26% of the variance in self-informant discrepancies, F (10, 129) = 4.09, p < .001.

In contrast to the other two FrSBe subscales, for the patient-informant discrepancies in the *Disinhibition* subscale, we found no significant association between the Executive Composite score and self-informant discrepancies in FrSBe Disinhibition ratings. Specifically, after controlling for demographic variables, UHDRS motor score, and HADS scores at Step 1, performance on the Executive Composite was not significantly related to self-informant discrepancies in FrSBe Disinhibition ratings at Step 2 (β = -.23, t = -1.41, p = .16). In fact, overall the model was not significant (F (10, 129) = .83, p = .60), and there were no significant predictors in the model.

In order to further explore these relationships, we also ran the same multiple regression analyses within the premanifest and early HD groups separately. We found that the same pattern of results in the early HD group but not the premanifest group. Specifically, for the FrSBe Executive Dysfunction subscale, in the early HD group, the Executive Composite score was the only predictor of self-informant discrepancies (β = -.48, t = -2.64, p = .01), with no other variables significant in the model. The model itself was significant, F (10, 59) = 2.09, p = .04. Similarly, for the FrSBe Apathy subscale, in the early HD group, the two significant predictors of self-informant discrepancies were the Executive Composite score (β = -.55, t = -3.0, p = .004) and HADS Depression score (β = -.36, t = -2.08, p = .04) . The overall model, however, just missed the statistical significance threshold (F (10, 59) = 1.90, p = .06). In contrast, for the premanifest group, there was no significant association between the Executive Composite score and self-informant discrepancies in either FrSBe Executive Dysfunction or Apathy, and the overall model was also not significant (all *ps* >.19). Finally, for the FrSBe Disinhibition subscale, there were no significant predictors of

self-informant discrepancies in either the premanifest or early HD groups, and the overall models were not significant.

INSERT FIGURE 2 HERE

Discussion

As hypothesised, self-informant discrepancies in FrSBe ratings did vary across the premanifest and early diagnosed HD groups, with premanifest HD participants tending to rate themselves as having relatively *more* neuropsychiatric symptoms than their informants rated them as having, consistent with previous studies of premanifest participants (Duff et al., 2010; Mason & Barker, 2015). Our findings expanded on those of Duff et al., as we demonstrated the same pattern of results in premanifest HD participants using the widely available 46-item version of the FrSBe. Interestingly, previous research has shown that healthy individuals tend to show this same bias when self-informant ratings are compared on the FrSBe (Barrett, McLellan, & McKinlay, 2013). This higher self-reporting of neuropsychiatric symptoms in comparison to informants may be because some of these symptoms relate to internal states that are more easily identified by an individual rather than their informant, or because anxiety about the development of HD symptoms may heighten awareness of one's own behaviours. In support of this, a recent study of self-awareness of symptoms after predictive testing for HD showed that 74% of premanifest carriers paid more attention to the presence of signs and symptoms related to the disease, 55% reported feeling anxious regarding their status, and 20% thought they had signs (Gargiulo et al., 2017). Another possibility is that that family members may be unwilling to acknowledge signs so early in the disease course, and therefore under-report neuropsychiatric symptoms. However, given healthy individuals show this same pattern of higher self-reporting of symptoms

compared to informants, we believe the higher self-ratings in premanifest HD are unlikely to suggest a true elevation in symptoms, unless it refers only to the subtle level of symptoms that are unrecognisable to close others.

In contrast, our finding that early manifest participants report *fewer, less severe* neuropsychiatric symptoms of apathy and executive dysfunction than their informants is consistent with previous studies of people with diagnosed HD, who under-report neuropsychiatric symptoms compared to informants (Chatterjee et al., 2005; Ho et al., 2006; Hoth et al., 2007). Unawareness of other symptoms, such as cognitive impairment and motor signs, have also been found in HD, and the results of our study indicate that at least for some early diagnosed individuals, a deficit in awareness of neuropsychiatric symptoms is also present (Ho et al., 2006; Hoth et al., 2007; Snowden, Craufurd, Griffiths, & Neary, 1998).

Our finding that participants who performed more poorly on executive tasks also showed unawareness of executive dysfunction and apathy indicates that cognitive status may be an important predictor of self-awareness of neuropsychiatric symptoms in HD. This interpretation is consistent with previous studies in HD that reported an association between cognition (particularly memory and executive function) and self-awareness of apathy (Chatterjee et al., 2005; Mason & Barker, 2015) or executive dysfunction (Ho et al., 2006). Our results, however, extend the previous findings, demonstrating for the first time, that this relationship is present across both premanifest and early HD stages, and that it is independent of demographic variables, motor and mood symptoms. In fact, in our study, participants' motor scores were not associated with unawareness of neuropsychiatric symptoms, a finding that remained even when premanifest participants, who have a restricted range of motor scores, were removed from the analysis. Our finding contrasts with Mason et al., who reported associations between motor scores and unawareness of apathy, however their study included early diagnosed to late disease stages (Mason & Barker, 2015). The relationship

between motor symptoms and awareness might be clear only later in the disease process, when both motor symptoms and unawareness of symptoms are more severe. Nonetheless, our findings suggest that in HD, people in both the premanifest and early diagnosed periods with executive impairment are likely to experience lower self-awareness of neuropsychiatric symptoms, regardless of the severity of their motor symptoms.

Our finding of a relationship between self-reported depression and self-awareness of apathy is consistent with that of Hoth and colleagues (Hoth et al., 2007), who found that HD participants who reported higher levels of depression also reported more behavioural and emotional symptoms compared to informants. One possible explanation for the relationship between awareness and mood in our sample is that unawareness represents denial as a psychological coping mechanism (Sitek et al., 2014). According to this theory, by denying the presence of symptoms that indicate the onset of a fatal disorder, participants protect themselves from the psychological distress associated with this knowledge. Our finding that higher unawareness was associated with less self-reported depression supports this hypothesis. In our study, however, the relationship between depression and self-awareness was specific only to awareness of apathy, and not other neuropsychiatric symptoms. Apathy measures often have complex relationships to other symptoms. For example, in HD apathy can manifest both in the context of depression, as well as a standalone symptom of the disease. Because apathy is more strongly related to cognitive impairment than depression in HD (Baudic et al., 2006), an alternative explanation to denial as a psychological coping mechanism is that executive dysfunction and consequent unawareness of one's symptoms is more likely to occur in HD when apathy is a standalone symptom, rather than when apathy arises in the context of depression. Instead, in the context of depression, self-awareness may be better maintained, allowing recognition of apathy in oneself, as an internal state, which

may be invisible to informants. Future research should more closely examine the relationships between unawareness, mood, and coping.

Unexpectedly, we did not find that executive performance was associated with self-awareness of disinhibition symptoms, despite finding a significant difference in self-informant discrepancies between premanifest and HD groups, indicating a reduction in self-awareness of disinhibition in HD. One possibility is that in our study, disinhibition levels, and consequently discrepancies in reporting disinhibition, were insufficient to reveal relationships with executive performance. Including later stages of HD, or recruiting specifically for people with disinhibition symptoms, might enable the identification of factors that relate to self-awareness of disinhibition.

When we examined the predictors of self-informant discrepancies in the early HD and premanifest groups separately, we found similar findings in the early HD group to the overall sample, but not in the premanifest group. One explanation for this difference is that both unawareness and cognitive difficulties are more common and severe in the early HD group than in the premanifest HD group, and therefore these relationships only become apparent once a particular threshold for impairment is reached. These smaller sample size of the subgroups mean that these subgroup analyses were strictly exploratory, however, and future research should therefore test this hypothesis with larger samples of premanifest and early HD participants.

Strengths of this study are the large sample sizes and the inclusion of both premanifest and early diagnosed HD participants. In terms of limitations, because this project was a secondary analysis of baseline data from TRACK-HD study, our design was limited by the measures available for analysis. Executive function has many specific elements, and different executive measures, had they been available, may have shown stronger relationships to self-awareness in HD. Alternatively, cognitive domains other than executive function may

also show an association with unawareness. Future studies should examine the relative predictive power of different types of executive function ability, as well as additional cognitive domains, on self-awareness in HD. Second, only the neuropsychiatric symptoms of executive dysfunction, apathy, and disinhibition were measured in the current study, when other neuropsychiatric symptoms, such as irritability, are also common. Future research should extend our findings to self-awareness of other types of symptoms in HD. Third, while our approach of using self-informant comparisons to assess awareness is common in HD, more objective measures of self-awareness could reveal additional insights. Finally, the question of how caregiver factors such as burden and mood influence informant ratings of neuropsychiatric symptoms is unknown and would be a valuable addition to this literature.

Taken together, our findings indicate that unawareness of neuropsychiatric symptoms is more common in early HD compared to premanifest HD, and that unawareness reflects an executive impairment, rather than general disease progression. Further, self-awareness of apathy may be intact when apathy is a symptom of depression, rather than when apathy appears as a standalone syndrome. These findings have important implications for clinicians, both for the accurate assessment of neuropsychiatric symptoms in premanifest and early HD, and education for patients and families.

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TABLE 1. Baseline participant characteristics

	Healthy Controls	Pre-HD	Early HD
N	119	60	72
Age (years)	46.33 (10.32, 23-66)	40.20 (9.25, 19-60)	49.94 (10.60, 23-64)
Women	65 (55%)	37 (62%)	33 (46%)
Education			
Primary/Middle School	24 (20%)	11 (18.4%)	16 (22%)
High School	13 (11%)	14 (23.3%)	16 (22%)
Technical college	35 (29.5%)	14 (23.3%)	13 (18%)
University Degree	47 (39.5%)	21 (35%)	27 (38%)
CAG repeat length	-	43.57 (2.84, 39-52)	43.61 (3.20, 39-59)
Disease- burden score	-	302.38 (50.79, 171.5-391.5)	378.11 (68.34, 210-551)
Centres			
Leiden	30 (25.2%)	18 (30%)	18 (25%)
London	29 (24.4%)	11 (18.3%)	17 (23.6%)
Paris	30 (25.2%)	10 (16.7%)	13 (18%)
Vancouver	30 (25.2%)	21 (35%)	24 (33.4%)
UHDRS TMS	1.47 (1.71, 0-7)	2.58 (1.38, 0-4)	24.29 (12.01, 5-52)
UHDRS TFC	12.98 (.13, 12-13)	12.75 (.70, 9-13)	10.65 (2.10, 7-13)
HADS Anxiety	5.21 (3.67, 0-17)	5.45 (3.26, 0-13)	6.85 (4.14, 0-20)
HADS Depression	2.86 (2.83, 0-11)	3.03 (3.19, 0-13)	3.88 (3.47, 0-18)
FrSBe Self – Exec	29.07 (7.90, 17-53)	34.20 (9.83, 14-58)	36.77 (10.41, 17-57)
FrSBe Self – Apathy	24.23 (6.47, 14-43)	27.60 (8.13, 14-49)	30.0 (9.48, 15-59)
FrSBe Self – Disinhibition	24.60 (5.69, 15-41)	25.92 (6.55, 15-41)	26.88 (7.38, 15-45)
FrSBe Informant – Exec	-	31.10 (10.18, 17-54)	42.97 (13.54, 19-72)
FrSBe Informant – Apathy	-	25.38 (8.00, 14-46)	33.45 (10.92, 16-60)
FrSBe Informant – Disinhibition	-	23.12 (6.96, 15-49)	27.64 (7.30, 15-46)

Data are mean (SD, range) or number (%). UHDRS TMS – UHDRS Total Motor Score: Possible scores range from 0 – 124; UHDRS TFC – UHDRS Total Functional Capacity: Possible scores range from 0-13; HADS – Hospital Anxiety and Depression Scale. FrSBe – Frontal Systems Behavior Scale; Exec – Executive Dysfunction

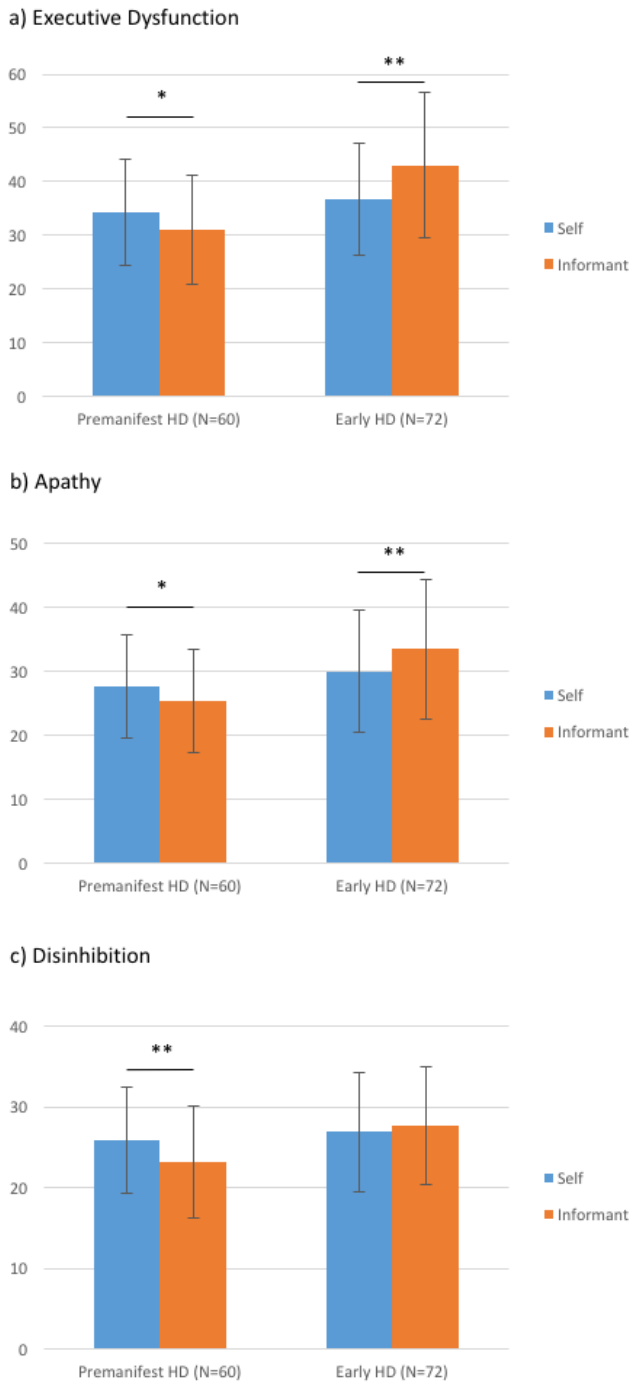

Figure 1. Premanifest and early HD group means (standard deviations) of self- and informant-ratings on Frontal Systems Behavior Scale subscales: (a) Executive Dysfunction (b) Apathy, and (c) Disinhibition. **p<.01; *p<.05

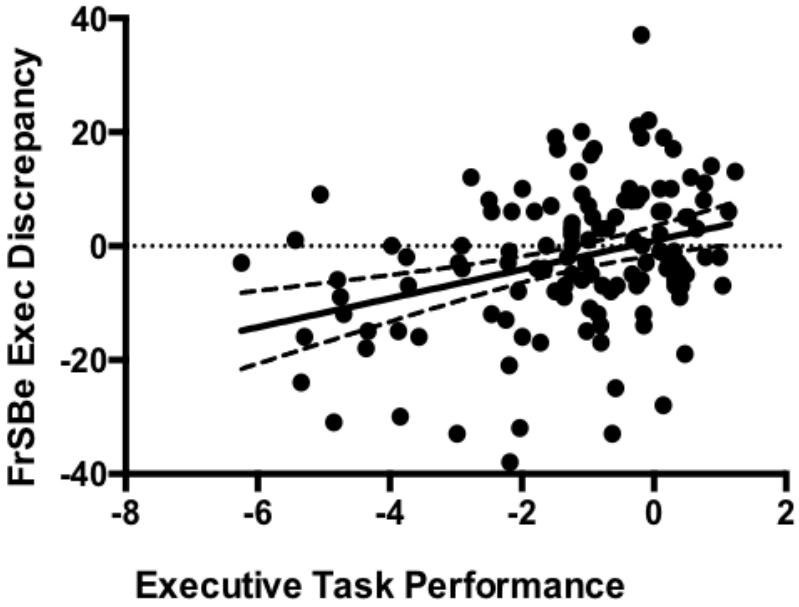

Figure 2: Relationship between Executive task performance and discrepancy between self and informant-ratings on FrSBe Executive Dysfunction subscale across the whole premanifest and early HD group (N=132), where better task performance is associated with higher self-ratings of Executive Dysfunction in comparison to informant-ratings.