Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

Multidimensional Apathy: The Utility of the Dimensional Apathy Scale in Huntington's Disease

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Abstract: Background: Apathy is a disorder of motivation common to Huntington's disease (HD). Recent conceptual frameworks suggest that apathy is not unitary but consists of discrete subtypes ("dimensions"). Which of the proposed dimensions are preferentially affected in HD, and how these dimensions evolve with disease progression is unknown.

Objectives: The Dimensional Apathy Scale (DAS) separates apathy into Executive, Initiation and Emotional subscales. Using the DAS, we aimed to: 1) Determine the apathy subtypes prevalent in HD; 2) Compare the DAS against a unitary measure of apathy (Apathy Evaluation Scale, AES); 3) Assess the reliability of self- and observer-ratings; and 4) Determine the relationship between the DAS, and disease burden, total functional capacity (TFC) and the AES.

Method: Fifty pre-manifest, 51 manifest-HD, 87 controls, and 50 HD-observers completed the DAS, AES, and TFC.

Results: Manifest-HD participants had the highest levels of apathy across all dimensions (30.4% on Executive subscale, 34.8% on Initiation subscale, and 15.2% on Emotional subscale), relative to pre-manifest and control participants. Self- and observer-ratings on the DAS did not differ. Hierarchical regressions across the entire gene-expanded sample showed that scores on the Initiation subscale correlated with AES scores; higher Executive subscale scores were related to higher disease burden; and Emotional subscale scores with lower total functional capacity.

Conclusions: In this first study of the DAS in HD, manifest-HD participants were more apathetic than pre-manifest and control participants across all apathy subtypes. The DAS may be a useful tool for measuring different aspects of apathy in people with HD.

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by an expanded CAG triplet repeat on the *huntingtin (HTT)* gene.[1] HD typically develops in midlife, with degeneration first observed in the dorsal striatum, before progressing to the ventral striatum and frontal limbic circuits.[2,3] This neural degeneration results in a triad of symptoms that include motor dysfunction, cognitive decline and neuropsychiatric changes. Although the diagnosis of manifest-HD is made on the basis of motor signs,[4] gene-expansion carriers also experience neuropsychiatric symptoms, such as apathy, up to 15 years prior to diagnosis.[2,5–8]

Apathy is a disorder of motivation, characterized by a reduction in goal-directed behavior, and occurs both as a symptom of depression and as a neuropsychiatric syndrome in isolation.[9–13] In HD, apathy is a disabling and common behavioral symptom, associated with disease progression, poorer quality of life, reduced functional independence, and cognitive decline.[11,14–18] Apathy in HD is believed to be driven by the involvement of

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frontostriatal circuits that facilitate motivated behavior, such as the medial pre-frontal cortex and ventral striatum.[19,20,21] In pre-manifest gene-expansion carriers the incidence of clinically significant apathy is as high as 26.9%,[22] and up to 63% in early manifest-HD.[7] These rates of apathy reflect the progressive involvement of frontostriatal circuits with disease progression.

Recent theoretical frameworks consider that apathy may be evident across separate dimensions that differentially affect daily functioning (ie, cognitive, behavioral, emotional).[9,12,23] These frameworks are consistent with neurophysiological, neuroimaging and human lesion studies, which have implicated separable networks for different domains of motivation (eg, the amygdala and dorsolateral prefrontal-cortex in cognitive apathy).[19,21,23] Despite the evidence for separate subtypes of apathy, multidimensional tools have previously been limited to clinician-administered interviews (eg, the Lille Apathy Rating Scale[24]) and most self-report inventories yield only a total apathy severity score, which does not allow us to assess apathy across these separate putative subtypes (eg, the Apathy Evaluation Scale (AES), Apathy Scale, Frontal Systems Behavior Scale, Problem Behaviors Assessment-HD).

One exception is the Dimensional Apathy Scale (DAS), which specifically quantifies three subtypes of apathy:[25] (1) Executive (disrupted planning, attention and organization); (2) Emotional (blunted emotional responses); and (3) Initiation (loss of spontaneous activity). The DAS has been particularly useful in distinguishing different profiles of apathy across neurodegenerative disease. For example, apathy in Amyotrophic Lateral Sclerosis (ALS) is driven by Initiation apathy; Executive apathy is typically spared in Parkinson's Disease (PD);[26–28] and apathy in Alzheimer's disease (AD) affects all dimensions of apathy.[26,29]

The prevalence of different subtypes of apathy in HD, and how they evolve with disease progression, remains unknown. This is an important omission from the literature, as understanding the contribution of apathy subtypes to HD could facilitate more targeted research and interventions.[30–33] The assessment of apathy by self-report also poses a challenge, as a loss of insight often occurs in HD, rendering self-reports inaccurate. For example, our group has documented discrepancies between self- and observer-rated apathy in HD,[15] with observers typically rating apathy symptoms as more severe than manifest patients' self-reports. Whether reduced insight expresses differently for apathy subtypes in HD is unknown.

In this study, we used the DAS to examine apathy subtypes in pre-manifest and manifest-HD compared to healthy controls. The aims of our study were: (1) characterize the apathy syndrome in HD across the three DAS subscales; (2) examine the convergent validity of the DAS against a common and widely used apathy self-report measure that provides only a total summed score of apathy, the AES; (3) determine the consistency between self- and observer-ratings of apathy (ie, interrater reliability); and (4) assess the convergent validity of the DAS subtypes with measures of disease impact. We hypothesized that total apathy scores on the AES and DAS would be strongly correlated, but that the DAS would further differentiate apathy subtypes in pre-manifest and manifest-HD,[19] with dissociable relationships between clinical measures of disease. Finally, we expected discrepancies between self- and observer-rated apathy on the AES and the DAS.

Method

Participants

The sample comprised 238 people, who self-identified into one of the following groups: pre-manifest HD (n = 50), manifest-HD (n = 51), and controls who were either gene-negative (n = 87) or HD family members not at genetic risk (n = 50). Participants completed an online survey that included several standardized questionnaires (Table 1), along with questions pertaining to their demographic and clinical information. We used online advertisements and flyers to recruit people from local health care providers, HD state organizations in Australia and the USA, and a Monash University (Melbourne) internal research database. The final sample included people from Australia (n = 217), New Zealand (n = 3), the USA (n = 17) and the UK (n = 1).

Criteria for inclusion were age over 18 years, and, in the HD group, participants were asked to confirm that they had undergone genetic testing confirming that they had the *HTT* gene expansion. We obtained the genetically verified CAG expansion data of participants recruited from our Monash University internal database, allowing us to confirm abnormal *HTT* in 73 (75%) of the gene-expanded HD group.

The online survey included a series of screening questions, allowing us to exclude participants who endorsed a history of neurological disease (other than HD), major traumatic brain injury, cerebrovascular accident, or substance use disorder. The survey directed excluded respondents to the survey end without presenting any of the standardized apathy measures. We excluded HD observers if they did not have a HD family member participating in the study (n = 12). Of HD participants with observers, the most common relationship was a spouse (82%). This study received approval from the Monash University Human Research Ethics Committee (MUHREC), and all participants provided informed consent in accordance with the Declaration of Helsinki.

Procedure

The online questionnaire, hosted on the survey platform Qualtrics (Provo, UT; available at https://www.qualtrics.com), comprised the following: (1) explanatory statement and consent form; (2) screening and demographic questions; (3) the DAS;[25] (4) the AES,[34] and; (5) the Hospital Depression and Anxiety Scale (HADS).[35] The pre-manifest and manifest-HD groups, along with their observer also completed a self- and an observer-reported version of the Total Functional Capacity scale (TFC) created for the purpose of this study (see materials).[36]

TABLE 1 *Summary of demographic and disease related variables (means (SD))*

	Healthy Controls	Pre-Manifest HD	Manifest HD
N	87	50	51
Gender (M: F [a])	38:49 (56%)	21:29 (58%)	29:22 (43%)
Age in years [Range]	46.60 (17.92) [18–82]	42.70 (13.40) [23–75]	52.28 (11.64) [20–77]
Years of education	15.06 (2.30)	14.10 (2.57)	13.22 (1.89)
CAG [Range]	–	40.87 (2.00) [38–45]	42.77 (2.35) [39–54]
Total Functional Capacity [b] [Range]	–	12.72 (.95) [8–13]	8.73 (2.59) [4–13]
Disease Burden Score (DBS) [c] [Range]	–	229.53 (94.63) [65–435]	378.04 (77.12) [192.50–518]
Total Motor Score (UHDRS) [d] [Range]	–	1.7 (2.83) [0–12]	20.38 (9.84) [5–45]
Apathy Evaluation Scale [Range]	28.28 (6.55) 18–44	30.96 (9.24) 19–58	36.76 (12.22) 19–66
Dimensional Apathy Scale [Range]	22.66 (6.98) [7–42]	24.18 (10.85) [3–61]	35.49 [11–65]
Executive [Range]	6.37 (3.55) [0–17]	6.70 (5.39) [0–23]	11.59 (5.92) [0–22]
Initiation [Range]	8.31 (3.36) [1–16]	9.18 (4.84) [0–22]	13.08 (5.13) [2–22]
Emotional [Range]	7.98 (3.70) [0–19]	8.30 (3.65) [0–17]	10.82 (4.05) [1–22]
Hospital Anxiety and Depression Scale			
Anxiety [Range]	5.83 (3.50) [0–17]	6.58 (3.96) [0–16]	6.84 (4.43) [1–19]
Depression [Range]	3.18 (2.92) [0–12]	3.36 (3.52) [0–16]	6.04 (4.37) [0–16]

Figures in parentheses represent standard deviation unless otherwise indicated.
[a]Percentage of females.
[b]Lower scores indicate a higher level of functional disability.
[c]DBS = (CAG-35.5) · age.
[d]Unified Huntington's Disease Rating Scale Total Motor Score has a maximum score of 124. Higher scores indicate more motor symptomatology.

Materials

Dimensional Apathy Scale (DAS)

The DAS is a self-report measure of apathy that minimizes somatic questions related to motor disability.[27] The scale comprises three distinct subscales of apathy, termed "Executive" (eg, "I find it difficult to keep my mind on things"), "Initiation" (eg, "I act on things I have thought about during the day"), and "Emotional" (eg, "I am indifferent to what is going on around me"). Each subscale consists of eight items, rated on a 4-point Likert scale, leading to a maximum subscale score of 24 and a total score of 72. Higher scores reflect greater apathy. Self- and observer- rated versions of the DAS are available.[25,27] Cut-off scores are available for people with ALS and PD; there are currently no cut-off scores for people with HD.

Apathy Evaluation Scale (AES)

The AES comprises 18 items, rated on a 4-point likert scale that produces an overall apathy rating ranging from 18 (lowest apathy) to 72 (highest apathy). The AES has been validated in a range of clinical populations, including HD,[11,37–41] and has been recommended by the International Parkinson's Disease and Movement Disorders society for screening symptom severity in HD.[42] Both self- and observer-rated versions of the AES are available. The recommended AES cut-off score to identify clinically abnormal apathy is 41 (>2 standard deviations above the normative mean),[27,34] which was consistent with the data from our control sample. Using this cut-off, 38% of the manifest-HD respondents endorsed elevated apathy, a proportion that was significantly higher than pre-manifest (18%) and control (6.9%) participants ($P < 0.001$). Thus, overall for our sample, less than half of HD participants endorsed apathy levels above what we considered clinically significant.

Hospital Anxiety and Depression Scale (HADS)

The HADS is a self-report scale of depression and anxiety comprised of 14 items that produce two seven-item subscales, with scores ranging from zero to 21. Items target affective symptoms of mood disturbance, excluding somatic and cognitive symptoms that may otherwise artificially inflate depression scores in HD.[42] The recommended subscale cut-off score to identify moderate depression or anxiety is 11, and scores above 15 indicate severe symptomology.[35] According to these cut-offs, 20% of manifest-HD respondents reported moderate to severe symptoms of depression, compared to 4.0% of pre-manifest participants and 1.1% of controls. We used the HADS Depression subscale score as a covariate in our regression analyses to examine the impact of apathy independent of depression.

Total Functional Capacity (TFC) of the Unified Huntington's Disease Rating Scale (UHDRS)

The TFC is a 5-item clinician-rated measure of functional activity in HD[36] that assesses engagement in occupation, finances, domestic chores, personal care, and required professional supports. Respondents rate items on a 0–2- or 0–3-point scale to produce an overall score of zero to 13, with higher scores indicating more functional independence. TFC scores partition HD progression into five stages: scores from 11–13 represent stage I (early); 7–10, stage II (middle); 3–6, stage III (moderate); 1–2, stage IV (late) and 0, stage V (end).[36,43] We included the TFC items online and asked HD participants and their observers to rate their current level of functioning because obtaining clinician-rated TFC scores was not feasible. This online methodology has been used in other HD studies with success.[44] In our sample, HD participants had Total Functional Capacity (TFC) scores ranging from 13 (fully independent functioning) to 5 (moderate disease stage, requiring some assistance with activities of daily living). The Pearson correlation between self- and observer-ratings was *excellent* (r = .92, $P < 0.001$), and this level of agreement occurred for participants in pre-manifest and manifest disease stages (Group x Disease Stage Interaction ($F(1, 96)$ = .265, $P = 0.608$, η^2 = .003).

Disease Burden Score

We derived a disease burden score (DBS) for the 73 ($n_{\text{pre-manifest}}$ = 35; $n_{\text{manifest-HD}}$ = 38) participants for whom genetic data was available, based on the commonly used calculation: (CAG-35.5) · age.[45] We used DBS scores as a proxy measure of disease severity in our regression model.

Participant Demographics

HD groups and controls were similar in gender distribution ($P = 0.237$). As expected, the manifest-HD group was significantly older than the pre-manifest HD ($P = 0.006$) group but not the control group ($P = 0.457$). Pre-manifest and manifest-HD participants did not differ in years of education ($P = 0.156$). Controls reported more years of education than the manifest-HD ($P < 0.001$) and pre-manifest HD groups, although the latter did not reach statistical significance ($P = 0.056$) (Table 1). When we examined the bivariate correlations between education and both AES and DAS total and subscale scores, the associations were weak ($r = -.25$ or less), thus we did not adjust for education in our analyses.

Statistical Analyses

Using SPSS statistics V.26 (IBM) we conducted independent t tests, chi-square tests, and one-way and mixed-model ANOVAs to compare pre-manifest gene-expansion carriers, manifest-HD, and control participants on a range of demographic and disease-related variables. We used Pearson correlation coefficients to assess levels of agreement between self- and observer-rated apathy and Bonferroni-corrected group comparisons to examine significant main effects and interactions. When examining the relationship between disease-related functional decline and distinct apathy subtypes, we studied the disease as a continuum, using hierarchical multiple regression models across the entire gene-expanded sample. In these models, we examined R^2 values to determine which apathy subscale explained the most variance in our outcome scores. In both models, we entered age and depression as covariates and winsorized two univariate outliers.

Results

Interrater Reliability between Self- and Observer-Rated Apathy

Interrater reliability for the DAS total scale was *good* with a correlation coefficient of .70, $P < 0.001$. Self- and observer-rated apathy did not significantly differ ($F(1,96)$ = .91, $P = 0.343$, η^2 = .009). This agreement did not vary by disease stage (Group x Disease Stage interaction, $F(1,96)$ =1.68, $P = 0.200$, η^2 = .02), and apathy scores were significantly higher in manifest compared to pre-manifest HD participants ($F(1,96)$ = 57.95, $P < 0.001$, η^2 = .38). In contrast, ratings on the DAS differed as a function of apathy subtype ($F(2,192)$ = 17.26, $P < 0.001$, η^2 = .15), which was further qualified by a significant interaction between disease stage and subtype ($F(2, 192)$ = 6.96, $P = 0.001$), although the effect was small (η^2 = .07) (Fig. 1B). Decomposing this interaction revealed that manifest-HD participants experienced similar levels of apathy across all subscales, whereas pre-manifest participants reported significantly less Executive, relative to Initiation ($P < 0.001$, d = 1.20) and Emotional, apathy ($P < 0.001$, d = 1.23). Although these results are cross-sectional, they may suggest that the Executive apathy subtype develops at later stages of the disease.

Consistent with the DAS, interrater reliability of the AES was *good* with a correlation coefficient of .67, $P = 0.001$. Similar to the DAS, the manifest-HD group had significantly higher rates of apathy than their pre-manifest counterparts (Disease Stage: ($F(1, 96)$ = 32.64, $P < 0.001$, η^2 = .25), but self- versus observer-rated scores did not differ ($F(1,96)$ = .30, $P = 0.589$, η^2 = .003). This agreement did not differ as a function of disease status (Disease Stage x Group interaction; $F(1,96)$ = .899, $P = 0.345$ η^2 = .009)(Fig. 1A).

Comparisons between Groups on Self-Reported Apathy Assessed by the DAS and AES

Given acceptable agreement between self- and observer-rated apathy, we used a 3x3 mixed model ANOVA to compare self-reports of pre-manifest, manifest, and control participants on the

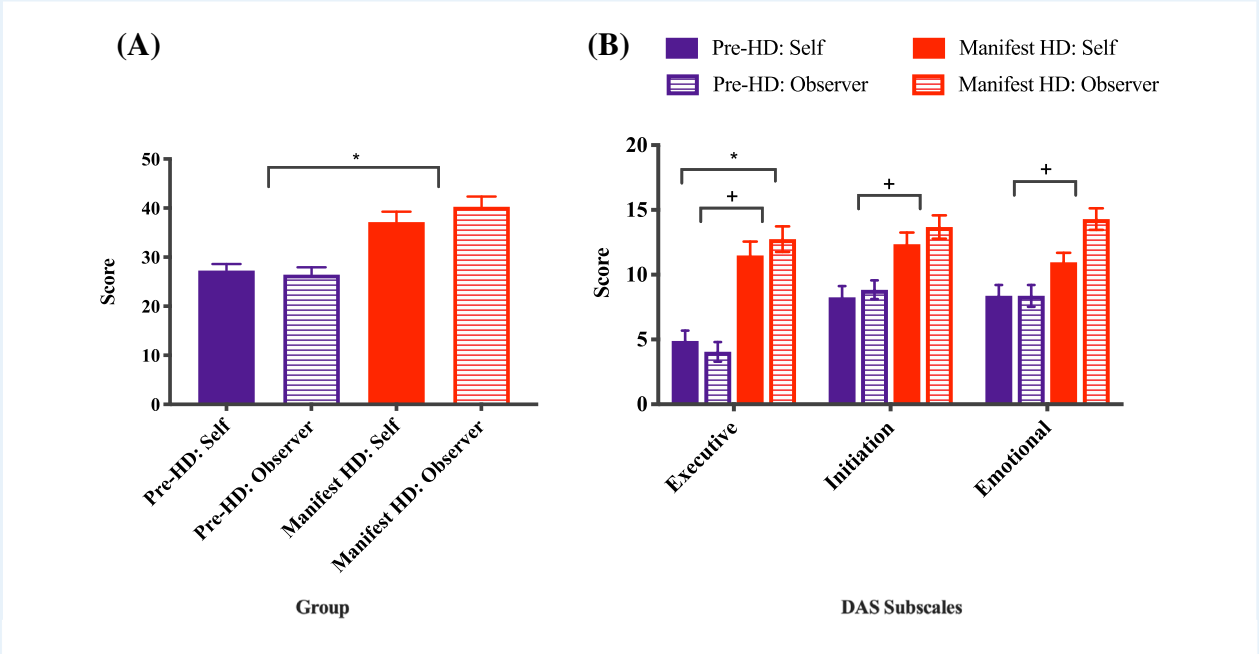

FIG. 1. Self- and observer-rated apathy on the AES and DAS across pre-manifest HD and manifest-HD groups. (A) Self- and observer-rated apathy measured on the Dimensional Apathy Scale (DAS) $^{+}$ Indicates significant main effect between pre-manifest and manifest groups. *Indicates significant interaction between Disease Stage and DAS Subscales. (B) Self- and observer-rated apathy measured on the Apathy Evaluation Scale (AES). *Indicates significant main effect of Disease Stage. Error bars represent standard error.

DAS (Fig. 2B). A main effect of group revealed that manifest-HD participants reported higher rates of apathy than their pre-manifest counterparts and controls, with a large effect size ($F(2,185) = 30.51$, $P < 0.001$, $\eta^2 = .25$). In contrast, ratings of apathy did not differ between pre-manifest participants and controls ($P = 1.0$). DAS subscale scores did not differ as a function of group membership, although the interaction was approaching significance (DAS x Group Interaction ($F(4,370) = 2.36$, $P = 0.053$, $\eta^2 = .025$). The analogous univariate ANOVA with the AES was consistent with the DAS; a significant main effect of group was revealed ($F(2,184) = 13.88$, $P < 0.001$ $\eta^2 = .131$), with manifest-HD participants scoring higher on the AES than controls (Fig. 2A).

Comparison of Rates of Clinical Apathy across Groups

To determine appropriate DAS clinical cut-off scores, we took a subset of 43 control participants who were similar in age and education to the manifest-HD group ($P = 1.0$ and .504 respectively). We then calculated DAS cut-off scores to indicate two standard deviations above the matched control group mean (provided in Table 2). Based on our cut-offs, 43.1% of manifest participants were clinically apathetic, which was significantly more than the proportion of apathetic pre-manifest (10.0%) and control (1.1%) participants ($P < 0.001$). Similarly, the proportion of clinically apathetic participants in the pre-manifest HD group was higher than the proportion of apathetic control participants ($P < 0.001$) (Fig. 2C). 52.9% of manifest-HD participants had abnormally high scores on at least one DAS subscale, compared to 20.0% of pre-manifest participants and 10.3% of control participants. Figure 2D shows the proportion of clinically apathetic participants on each subscale of the DAS.

Associations between DAS and Other Sample Characteristics

We used hierarchical regression, with age and depression entered as covariates in the first step, to examine the relationship between the AES and the DAS subscales, which were entered in the second step. We found that higher levels of self-rated depression were associated with higher ratings of apathy on the AES. Higher AES scores were also uniquely associated with greater DAS Initiation subscale scores ($F(5,94) = 78.85$, $P < 0.001$), accounting for 81% of the variance. In contrast, Executive and Emotional apathy subscales did not uniquely account for any of the variance (see Table 3 for Beta coefficients).

Next, we used hierarchical regression to examine relationships between apathy subtypes and disease burden, separating the variance due to age and depression by entering them in the first step, and then entering DAS subscales in the second step.

DAS subscales accounted for 39% of the variance in DBS ($F(5,66) = 8.31$, $P < 0.001$). Specifically, the Executive subscale was associated with higher DBS, whereas the Initiation and Emotional subscales were not significantly associated (Table 3).

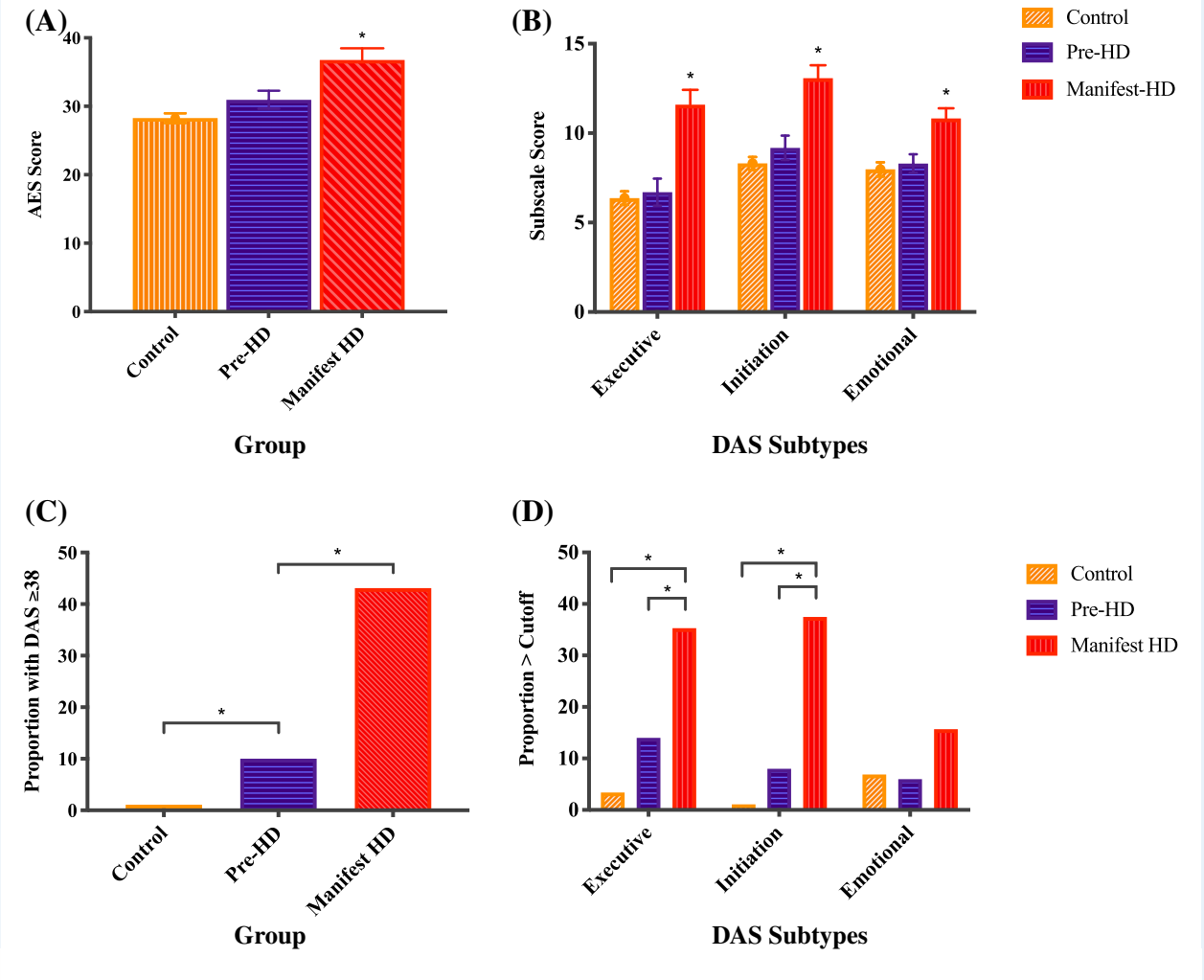

FIG. 2. Self-reported apathy on the AES and DAS across control, pre-manifest HD and manifest-HD groups. Top row (A and B) denotes self-reported apathy on the AES and DAS across control and, pre-manifest and manifest HD groups. (A) Control, pre-manifest (pre-HD) and manifest HD self-reported apathy on the Apathy Evaluation Scale (AES). (B) Control, pre-manifest (pre-HD) and manifest HD self-reported apathy scores on the Executive, Initiation and Emotional subscales of the Dimensional Apathy Scale (DAS). Bottom row (C and D) denotes the proportion of respondents with clinically high apathy across controls and, pre-manifest and manifest HD groups. (C) Clinically relevant apathy defined as a DAS total score of ≥38. (D) Clinically relevant apathy on the DAS subscales defined as a score of ≥13 on Executive, ≥16 on Initiation, and ≥ 16 on Emotional, subscales. * $P < 0.001$. Error bars represent standard error.

Finally, we used hierarchical regression to examine relationships between specific apathy subtypes and functional capacity on self-rated TFC. We separated the variance due to age and depression by entering them in the first step, and then entered DAS subscales in the second step. We found a significant change in R^2 after the addition of DAS subscales, accounting for 45% of the variance in TFC. We found that higher Emotional apathy scores were associated with lower functional capacity ($F(5,94) = 15.53$, $P < 0.001$), whereas the Initiation and Executive subscales did not uniquely account for TFC (Table 3).

TABLE 2 *Normative data for the DAS (N = 43)*

	Mean (SD)	Range	Abnormality cut-off
DAS Executive subscale	5.67 (3.78)	0–13	≥13
DAS Initiation Subscale	9.05 (3.61)	1–16	≥16
DAS Emotional Subscale	7.88 (3.40)	0–17	≥15
DAS Total	22.61 (7.73)	7–34	≥38

DAS, Dimensional Apathy Scale. Maximum score for each subscale is 24. The maximum total scale score is 72. Cut-off scores are equal to two standard deviations above the matched normative mean.

TABLE 3 *Relationship between dimensional apathy subscales and AES, DBS and TFC*

AES (*N* = 100)					
Predictor	Unstandardised B	Standard Error	Standardized B	*t* statistic	*P*- value
Constant	19.446	2.294		11.453	<.001*
Age	−.067	.039	−.081	−1.718	.089
HADS-D	1.188	.206	.441	5.769	<.001*
DAS-Exec	.230	.129	.127	1.776	.079
DAS-Ini	.863	.147	.413	5.876	<.001*
DAS-Emo	.033	.151	.012	.216	.829
DBS (*N* = 73)					
Predictor	Unstandardised B	Standard Error	Standardized B	*t* statistic	*P*- value
Constant	23.986	49.982		.636	.527
Age	4.352	.854	.510	5.094	<0.001*
HADS-D	−8.718	4.487	−.316	−1.943	.056
DAS-Exec	8.932	2.820	.481	3.167	.002*
DAS-Ini	.419	3.201	.020	.131	.896
DAS-Emo	2.821	3.296	.100	.856	.395
TFC (*N* = 101)					
Predictor	Unstandardised B	Standard Error	Standardized B	*t* statistic	*P*- value
Constant	16.107	.970		16.609	<0.001
Age	−.032	.017	−.151	−1.907	.060
HADS-D	−.152	.087	−.225	−1.743	.085
DAS-Exec	−.102	.055	−.223	−1.856	.067
DAS-Ini	−.074	.062	−.142	−1.197	.234
DAS-Emo	−.149	.064	−.216	−2.337	.022*

AES, Apathy Evaluation Scale; DAS, Dimensional Apathy Scale; DBS: Disease burden score ((CAG-35.5) · age); Emo, emotional subscale; Exec, executive subscale; HADS-D, Hospital Anxiety Depression Scale – Depression subscale; Ini, initiation subscale; TFC, Total Functional Capacity. *significant predictor.

Discussion

In this first study to examine apathy subtypes in HD, we found that on the DAS, manifest-HD participants demonstrated higher Executive, Initiation and Emotional subtypes of apathy compared to pre-manifest and control participants. The higher levels of apathy measured on the DAS were mirrored by the AES, thereby demonstrating consistency in the sensitivity of the measures. The higher rates of apathy in *manifest* HD found here is consistent with past studies using the AES and clinician rated tools.[7,22,33] Levels of apathy in the *pre-manifest* group did not significantly differ from controls in our study. This may be attributable to some of the pre-manifest participants being far from motor onset, thus when combined as a group, those with mild or no signs of apathy may have appeared like healthy controls, diluting any group effect. Nonetheless, using our DAS cut-off scores we showed that clinical apathy was more prevalent in pre-manifest participants than controls. This prevalence is consistent with previous research reporting subtle signs of apathy throughout the pre-manifest period.[7] Our finding that DAS cut-off scores effectively separated manifest, pre-manifest and control participants suggests that this approach could facilitate early detection of apathy in HD. Early detection is essential, as apathy syndromes predict faster cognitive decline and functional impairment in HD,[31,46] and timely behavioral interventions in clinical settings to address these symptoms are vital. Importantly, our cut-off scores are consistent with those originally proposed by Radakovic and Stephenson[27] in an ALS sample, thereby supporting the generalizability of DAS cut-off scores.

The greater apathy in manifest-HD across all subscales is similar to that reported in behavioral variant frontotemporal dementia[47] and AD[29] but differs from other neurodegenerative diseases in which the DAS has been applied. For example, ALS appears to selectively result in Initiation apathy, whereas PD results in greater Emotional and Initiation apathy, while sparing the Executive domain.[26,27] The global apathy in HD is likely driven by the involvement of key neural areas that are involved in motivated behavior, such as the ventral striatum and medial prefrontal cortex. In addition, recent work suggests that cognitive (analogous to Executive) apathy has been associated with dorsolateral prefrontal cortex and amygdala dysfunction,[19,48,49] and Emotional apathy with orbitofrontal cortex lesions.[23] Collectively, these areas are progressively affected by the neuropathology of HD, which may explain the apathy across subtypes observed in our study.[2,5,6,50,51]

Unexpectedly, self- and observer-ratings were consistent on both the AES and DAS, suggesting that in this sample, people in pre-manifest and early to middle stage HD, recognized their apathetic behaviors as effectively as their partners. This agreement is consistent with other studies in HD,[22,44,52] as well as the original validation study of the DAS,[27] but contrasts with previous findings from our group.[15] In our previous work we showed a

relationship between insight and cognitive impairment and this association has been shown elsewhere, both in HD[52] and in other neurodegenerative diseases.[53] The discrepancy between studies may be explained by differences in cognition across samples. In this study, we did not obtain observer-ratings for control participants. Future studies may seek to obtain observer-ratings for both HD and control participants in order to compare the relative difference between self- and observer-ratings; an approach that has been adopted elsewhere.[54,55] Nonetheless, our findings suggest that HD patients may still be reliable reporters of neuropsychiatric symptoms such as apathy, particularly those with no more than mild–moderate symptoms.

The Initiation scale of the DAS overlapped greatly with the AES, providing strong evidence of convergent validity for this subscale. In contrast, the Executive and Emotional subscales of the DAS did not capture the apathy measured on the AES, suggesting that these subscales are, as intended, measuring different components of apathy.[23,25] This finding has important implications for studies that have used the AES to evaluate apathy and its clinical correlates in HD.[11,22,56] In these studies, the AES may have captured the components of apathy related to Initiation (spontaneous generation of behavior), while overlooking Executive and Emotional apathy. Future studies using the DAS will help to disentangle the relationship between apathy dimensions and the clinical correlates of apathy, such as cognition, quality of life and carer-burden.[14,17,57]

Consistent with past literature,[32] our results highlight the detrimental impact of Emotional apathy on functional independence. This finding fits with the disrupted fronto-limbic pathology of HD leading to impaired emotional regulation and a clinical phenotype characterized by flattened affect, impaired emotion recognition and reduced social engagement.[58–60] These deficits in social cognition worsen as the disease progresses, contributing to a loss of functional independence. Although our methodology precluded participation of people with late stage HD (ie, those with a TFC < 5), it is possible that a full range of TFC scores would strengthen this relationship, and future work could use observer-ratings of Emotional apathy in the late stages of disease to test this hypothesis.

We found that the Executive subscale of the DAS, which measures the aspects of apathy related to planning, was related to higher DBS scores. One reason for this relationship may be that this component of the DAS captured, not only the willingness of individuals to initiate a course of action, but also their capacity to plan it. This is possible as the frontostriatal regions associated with disease progression (eg, dorsolateral pre-frontal cortex) are also important in Executive apathy and executive functions such as planning, organization and complex attention.[61] Previous studies in PD and ALS support this suggestion, showing that in diseases in which the severity of pre-frontal cortex degeneration varies,[62,63] Executive apathy is not elevated relative to controls.[26,27]

Our results should be interpreted in the context of several caveats. First, our study design was cross-sectional, so conclusions of change over time are speculative. Recruitment bias is a limitation of all apathy research, in that people who voluntarily participate in research are less likely to show severe levels of apathy. The rates of apathy reported here are therefore conservative estimates, and those with severe forms of apathy or with late stage disease were not captured. As we performed this study online, we were unable to obtain information pertaining to cognitive impairment. Apathy and cognitive dysfunction are known to track with disease progression in HD[20,64] and further research is needed to understand how cognitive impairment is associated with performance on the DAS. Future research may also seek to replicate our clinical cut-off scores using a gold-standard clinical interview of apathy, to which DAS scores may be compared. This method has been adopted by others to facilitate sensitivity and specificity metrics.[26,65]

The effective measurement of apathy subtypes across disorders of varying etiology is critical to appropriate diagnosis and management of the syndrome.[66] In this study, we provide the first insights into the multidimensional presentation of apathy in HD using the DAS. This study suggests that the apathy syndrome in manifest-HD affects all domains of motivation, and that these subtypes evolve as a function of disease stage.

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Author Roles

1) Research Project: A. Conception, B. Organization, C. Execution; 2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

Atkins, K. J.: 1A, 1B, 1C, 2A, 2B, 3A, 3B.
Andrews, S. C.: 1A, 2C, 3C.
Chong, T. T-J.: 1A, 2C, 3C.
Stout, J. C.: 1A, 2C, 3C.

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Activity	Title	Payment	Timing
Clinical Study: Implementation of HD-CAB	Vaccinex Inc.: Signal-HD	Contract to Stout Neuropsych Pty Ltd, with subcontract to Monash University, total value approximately $520,777 AUD	May 2015 – April 2020
Consulting agreement	uniQure	Value not specified, estimated at less than $10: per annum	May 2018 to present
Consulting agreement	CHDI Foundation, Inc.	Value up to $60 K	June 2018 to present
Consulting agreement	Sage Therapeutics	Value up to $23,000	August 2019 to present

Medical Research Foundation, and the Society for Mental Health Research. J.C.S received grant funding from the Australian National Health and Medical Research Council (NHMRC), Leadership 2 Investigator Grant. J.C.S. is the director of a research company, Zindametrix, which supports clinical trial sponsors in the use of the HD-CAB and other cognitive testing in clinical trials, and provides consulting services regarding cognitive assessment in Huntington's disease to clinical trial sponsors via Stout Neuropsych Pty Ltd. The authors declare that there are no conflicts of interest relevant to this work.

Ethical Compliance Statement: The Monash University Human Research Ethics Committee provided formal approval for this study. Informed consent was obtained from all research participants prior to their involvement. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm this work is consistent with those guidelines. ■

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