Frequency and Pathophysiology of Apathy in Huntington Disease: A Systematic Review and Meta-Analysis

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Objective: Apathy is a common behavioral symptom of Huntington disease (HD). This systematic review describes current evidence on the pathophysiology, assessment, and frequency of apathy in HD.

Methods: This systematic review was conducted in accordance with PRISMA guidelines. Using a comprehensive search strategy, the investigators searched the MEDLINE, Embase, and PsycINFO databases. All studies that evaluated apathy in HD patients with a valid scale and reported apathy frequency or scores were included. Apathy scores were analyzed by mean or standardized mean differences in accordance with Cochrane guidelines.

Results: A total of 1,085 records were screened and 80 studies were ultimately included. The Problem Behaviors Assessment—Short was the most frequently used apathy assessment tool. Apathy frequency generally ranged from 10%–33% in premanifest HD to 24%–76% in manifest HD. A meta-analysis of 5,311 records of patients with premanifest HD showed significantly higher apathy scores, with a standardized mean difference of 0.41 (CI=0.29–0.52; $p<0.001$). A comparison of 1,247 patients showed significantly higher apathy scores in manifest than premanifest HD, with a mean difference of 1.87 (CI=1.48–2.26; $p<0.001$). There was evidence of involvement of various cortical and subcortical brain regions in HD patients with apathy.

Conclusions: Apathy was more frequent among individuals with premanifest HD compared with those in a control group and among individuals with manifest HD compared with those with premanifest HD. Considering the complexity and unique pattern of development in neurodegenerative disease, further studies are required to explore the pathophysiology of apathy in HD.

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Apathy is a common behavioral symptom of neurodegenerative diseases. The term is derived from the Greek word "apatheia," meaning without passion. In the 19th century, apathy entered the medical lexicon to describe indifference or inability to feel emotions (1). Other definitions such as loss of motivation, reduced goal-directed behavior, or a decrease in self-initiation of actions were proposed and subsequently added to the definition (2). The concept of apathy as a neuropsychiatric syndrome was first proposed by Marin in 1990 in an attempt to differentiate apathy from other clinical disorders. He suggested defining apathy as a separate clinical condition marked by "diminished motivation not attributable to the level of consciousness, cognitive impairment, or emotional stress" (3). In 1998, Levy et al. (4) showed that apathy did not necessarily correlate with depression and can be a separate clinical entity across different dementia groups. In the 2000s, research groups attempted to establish a consensus definition of apathy. Starkstein et al. (5) proposed one of the first diagnostic criteria for apathy, which was later revised by Robert et al. (6, 7).

Apathy is one of the most common neurobehavioral symptoms of Huntington disease (HD), which is an inherited neurodegenerative disease characterized by progressive movement disorders, cognitive impairment, and behavioral changes (8). HD is caused by an expanded cytosine-adenine-guanine trinucleotide repeat in the huntingtin gene (HTT) located on chromosome 4 (9). A recent analysis of the Enroll-HD database found apathy to be the most influential factor in working capacity among those with premanifest HD (10). Because patients with HD can be unaware of their symptoms (anosognosia), apathy may be underreported yet impose a great burden on caregivers (11, 12). Moreover,

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apathy has been strongly associated with the progression and prediction of functional decline in those with HD (13). Despite being a common and debilitating symptom, the pathophysiology of apathy is still not fully understood, and to date, no medication has been approved for this condition (14).

In this systematic review and meta-analysis, we aimed to provide a broad perspective on the available evidence regarding apathy in HD, including its frequency in patients with manifest or premanifest HD, its pathophysiology, the clinical instruments used for its assessment, and its association with other clinical domains of HD.

METHODS

Design

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (15). A protocol of the study was registered in the international prospective register of systematic reviews (PROSPERO; CRD42022296392).

Search Strategy and Information Sources

A search strategy was developed using the keywords "Huntington disease" and "apathy" and related keywords such as "motivation," "interest," "self-activation," "psychic akinesia," "athymia," and "abulia." A detailed search strategy can be found in appendix 1 of the online supplement to this article. The MEDLINE (via PubMed and OVID), Embase, and PsycINFO databases were searched in November 2021. To include all relevant data, we placed no limitations on the search, including date or language.

Eligibility Criteria and Selection Process

Titles and abstracts were screened by independent reviewers (S.A.Z., H.M.C., and K.S.R.), and the full texts of relevant articles were reviewed for eligibility. Animal studies, case reports, and conference abstracts were excluded during title and abstract screening. Disagreements were reconciled through discussion or by using the expert view of a third reviewer (E.F.S. or A.L.T.).

We included all studies that evaluated apathy in HD patients. The exclusion criteria were studies that did not use a valid scale for scoring apathy or that used a scale not specific for apathy, such as the Beck Depression Inventory (BDI), which evaluates loss of interest related to depression; studies that did not report the number of patients with apathy or the apathy scores for each group; and therapeutic or interventional studies.

Data Collection and Data Items

A predefined data extraction sheet was used to collect information such as sample size, staging of disease, type of assessment, apathy scoring, and number of cases. The primary outcomes were the apathy scores and the frequency of apathy. The secondary outcomes were the pathophysiology of apathy in HD and the association of apathy with other HD symptoms.

Risk of Bias Assessment

Given the heterogeneity of the included studies and the lack of a unified standardized risk of bias (ROB) assessment tool for various study designs, we designed a tool tailored for this study. We partially used the Newcastle-Ottawa Scale and a quality assessment tool developed by Collins et al. (16, 17). Our modified criteria contain three domains (selection, outcome, and comparability) and nine questions, with a total score ranging from 0 to 14 (see appendix 2 of the online supplement).

Data Synthesis

The meta-analyses were performed with Review Manager, version 5.4, in accordance with the guidelines of the Cochrane Collaboration (18). To extract the data from plots, we used WebPlotDigitizer, version 4.5 (19). Mean differences and standardized mean differences (SMDs) were calculated when the same or different apathy scales, respectively, were used. To compare different subgroups of HD patients, we synthesized a combined group using the means and standard deviations of each subgroup. Heterogeneity was assessed with Cochrane's Q test and was defined as an I^2 value $>50\%$ or a p value <0.05. We performed each meta-analysis with both fixed- and random-effects models and presented the most appropriate model based on heterogeneity and funnel plot asymmetry.

RESULTS

Study Selection and ROB Assessment

The initial search yielded 1,085 records (Figure 1). After the removal of duplicates, the remaining 621 records were screened, and 94 studies were selected for full-text review. Twenty-two studies were excluded based on the exclusion criteria (see appendix 3 of the online supplement), and 69 studies were included. Eleven studies were added by screening the reference lists of relevant articles. Ultimately, a total of 80 studies were included. A detailed description of included studies and the result of the ROB assessment are available in appendixes 4 and 5 of the online supplement, respectively.

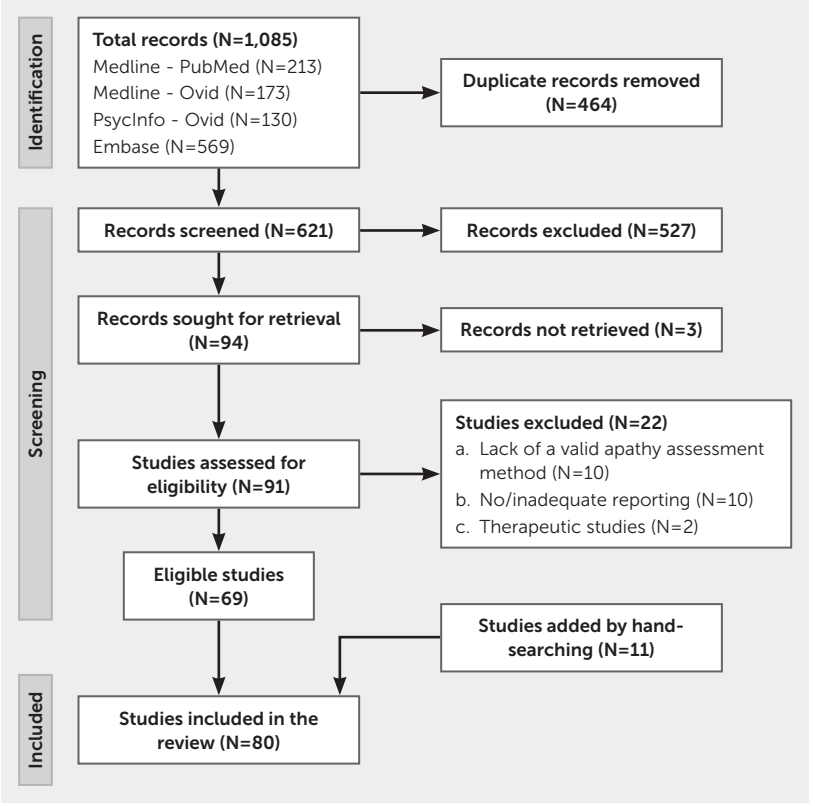
Apathy Assessment Tools in HD

Several tools have been used for apathy assessment. The scales are listed in order of historical development.

Irritability-Apathy Scale (IAS). The IAS is one of the oldest assessment tools for apathy (20). In addition to the original study, we found another study that used the IAS for the assessment of apathy in those with HD (21). The IAS is a semistructured interview performed by a clinician with an informed companion of a patient (20). It has two subscales: irritability (five items; total score range: 5–17) and apathy (five items; total score range: 5–25). Apathy is considered to be present when three or more items out of five are endorsed (20).

Apathy Evaluation Scale (AES) and Apathy Scale (AS). Seven studies used the AES (2, 22–27), and 11 used the AS (28–38). The AES was designed by Marin et al. with three versions, namely clinician (AES-C), informant (AES-I), and self-rated (AES-S), based on the source of information (39). The AES has 18 items with a 4-point scoring system (score range: 18–72) and is used to evaluate symptoms in the 4 weeks prior to the assessment. Despite some debate, a score of 40 or 41 has been used as the cutoff point for apathy in HD patients (2, 22, 26, 27). The AS is a shorter version of the AES that contains 14 items, and each item is rated from 0 to 3 points. A total score equal to or higher than 14 defines apathy (40). The AS was also used for the development of the Baltimore Apathy and Irritability Scale (BAIS) (37).

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the inclusion and exclusion of studies



Frontal System Behavioral Scale (FrSBe). This scale was originally developed as the Frontal Lobe Personality Scale (FLOPS) to assess behavioral changes in those with frontal dysfunction (41, 42). Eleven studies used the FrSBe for the assessment of apathy in HD patients (11, 41, 43–51). The FrSBe has three subscales, namely, apathy (14 items), disinhibition (15 items), and executive dysfunction (17 items), with each item rated from 1 to 5. For each of the three subscales, raw scores are converted to T-scores, which are corrected for age, education, and gender. A T-score of 65 or more is considered abnormal (42).

Neuropsychiatric Inventory (NPI). Four studies used the NPI (4, 52–54). This informant-based interview was designed to evaluate 10 neuropsychiatric symptoms over the previous 4 weeks by scoring the severity (1–3 points) and frequency (1–4 points) of each symptom (55). The magnitude of each behavior is calculated by multiplying the severity by its frequency. Caregiver distress is also rated from 0 (not distressing at all) to 5 (extremely distressing) for each positive symptom. The Neuropsychiatric Inventory Questionnaire (NPI-Q) was subsequently developed by adding two more items and removing the frequency assessment (56).

Unified Huntington's Disease Rating Scale Behavioral Scale (UHDRS-b). Seven studies used the UHDRS-b for apathy assessment in HD patients (57–63). The UHDRS evaluates four main domains, including motor, cognitive, behavioral, and functional independence (64). The behavioral domain originally comprised 10 items, and apathy appeared in the mood subdomain. In later versions, apathy became an independent item. Each item is rated on a scale from 0 to 4 for frequency and severity during the previous month. A score of 2 or more is considered an indication of the presence of a symptom (64).

Problem Behavior Assessment for Huntington Disease (PBA-HD). The PBA-HD was used in eight studies (8, 27, 65–70). Based on the UHDRS-b, Craufurd et al. (8) adapted a more extensive 40-item tool with a similar 0–4 scale for severity and frequency. To maintain compatibility with the UHDRS-b, they defined the presence of a symptom by a score of 2 or more and limited the inquiry to the 4 weeks before the interview.

Problem Behavior Assessment–Short (PBA-s). The PBA-s was the most frequently used assessment for apathy in HD patients (32 studies) (10, 12, 13, 23, 29, 43, 63, 71–95). It is a short version of the PBA-HD with 11 items and has shown high reliability. It is the recommended apathy assessment instrument for most HD clinical trials (96).

Dimensional Apathy Scale (DAS). The DAS is a relatively new scale and was used in two studies (2, 22). The DAS was designed to minimize the impact of physical disability and to provide a multidimensional approach to apathy assessment (97). This scale has 24 items and three subscales: executive, emotional, and initiation apathy. Each item is scored on a 4-point Likert scale (range: 0–3). The recommended cutoff points for abnormal values in HD patients are ≥13 points

on the executive subscale, ≥15 points on the emotional subscale, ≥16 points on the initiation subscale, and ≥38 points for the total score (2). Self- and observer-rated versions of the DAS, as well as a brief version (b-DAS) with nine items, are currently available (98).

Lille Apathy Rating Scale (LARS). This scale includes 33 items divided into nine domains, all of which address different manifestations of apathy (99). The first three questions are rated −2 to 2, and the remaining questions are rated −1 to 1. The total score ranges between −36 and 36, with a higher score indicating more severe apathy. A short version (LARS-s) was also developed with a range of scores between −15 and 15 (100). The proposed cutoff scores for clinically relevant apathy are >−21 for the LARS and >−7 for the LARS-s (100). Only one study used the LARS-s with HD patients (80).

Effort-based decision-making tasks. Effort-based decision-making tasks measure the level of effort an individual dedicates to a specific reward. Atkins et al. (22) and McLauchlan et al. (23) applied effort-based tasks to assess apathy in HD patients. The patients showed impaired instrumental learning and blunted responses to loss but showed no alterations in reward-related effort (23). Patients with premanifest HD exhibited reduced cognitive effort, whereas physical effort was normal (22).

Questionnaires. Three studies reported apathy with results from the Non-Motor Symptoms Questionnaire (NMSQuest) (101) or HD Clinical Characteristics (HDCC) questionnaire (102, 103). The NMSQuest is a self-administered 30-item questionnaire that evaluates various nonmotor symptoms (104). The HDCC provides a qualitative assessment of the frequency and timing of HD symptoms and signs and is currently a core assessment instrument in the REGISTRY and Enroll-HD studies (105). Both questionnaires collect yes or no responses and do not assess the severity of apathy.

Apathy Frequency and Scores in Patients With Premanifest and Manifest HD

The clinical diagnosis of HD has been historically defined by the presence of motor signs consistent with HD. A diagnostic confidence level of 4 on the UHDRS (i.e., ≥99% confidence that the motor abnormalities are unequivocal signs of HD) has been consistent with manifest HD. Some studies have categorized the premanifest stage into PreHD-A and PreHD-B based on the estimated time since disease onset. PreHD-A is associated with an estimated disease onset of more than 10.8 years, whereas in PreHD-B, the estimated disease onset is less than 10.8 years (95). The total functional capacity (TFC) scale has been frequently used to categorize HD patients based on the severity of the functional decline. It assesses functional independence in five domains: occupation, finances, activities of daily living, domestic chores, and care level (106).

The frequency of apathy among patients with premanifest HD ranged from 10% to 33% (2, 45, 80, 82, 83, 87, 88), but one study reported apathy in 64% of PreHD-B patients (88). Among patients with manifest HD, apathy frequency ranged from 24% to 76% (2, 4, 8, 21, 27, 35, 36, 52–54, 76, 80, 82, 83, 86–88, 102).

To compare patients with premanifest HD with healthy control individuals, we included 5,311 records from 12 studies (2, 12, 22, 29, 30, 44, 45, 65, 69, 88, 91, 95). Compared to individuals in a control group, patients with premanifest HD had a significantly higher apathy score with an SMD of 0.41 (CI=0.29–0.52; $p<0.001$). However, there was a significant level of heterogeneity among the studies (I^2: 63%, $p<0.001$; Figure 2).

The comparison of PBA-s scores between patients with manifest and premanifest HD based on the data from seven studies comprising 1,247 patients (74, 82, 84, 88, 89, 91, 95) showed significantly higher apathy scores in the manifest group with a mean difference of 1.87 (CI=1.48–2.26; $p<0.001$) and an SMD of 0.52 (CI: 0.41–0.64; $p<0.001$). This analysis showed homogeneity among the studies ($I^2=0$, $p=0.71$; Figure 3).

Dimensions of Apathy in Premanifest and Manifest HD

Multidimensional assessments of apathy were performed in three studies (2, 22, 80). De Paepe et al. (80) combined items of the LARS-s in three domains: cognitive, emotional, and autoactivation. There were significantly higher apathy levels in the autoactivation domain in both premanifest and manifest HD groups than in the control group. The cognitive subscale was higher only in the manifest HD group, and the emotional subscale showed no significant difference among groups. Atkins et al. (2, 22) used the DAS to investigate dimensions of apathy, including executive, emotional, and initiation apathy. There were no significant differences between patients with premanifest HD and control individuals in any of the dimensions. However, the effort-based decision-making task showed lower cognitive motivation in patients with premanifest HD versus control individuals (22). Patients with manifest HD had higher DAS scores than those with premanifest HD and control individuals. Furthermore, by setting the DAS cutoff score at ≥38 points, the number of individuals with apathy was higher in the premanifest HD group than in the control group (2).

Correlations Between Apathy and Other HD Symptoms

Cognitive functioning. Several studies have reported negative correlations between apathy and cognitive function (21, 25, 26, 34, 36, 41, 43, 44, 70, 74, 75, 77, 79, 86, 103). In a recent study, Andrews et al. (77) used 12 primary cognitive outcome variables from nine cognitive tasks and showed that apathy was a predictor of cognitive decline in patients with premanifest HD. They found a similar correlation in patients with manifest HD, but apathy was a weaker predictor of cognitive decline compared to UHDRS motor scores (77). Migliore et al. (75) performed a repeated-measures analysis of UHDRS cognitive domain scores in patients with manifest HD for up to 2 years of follow-up. There was a significant correlation between PBA-s apathy scores and the severity of

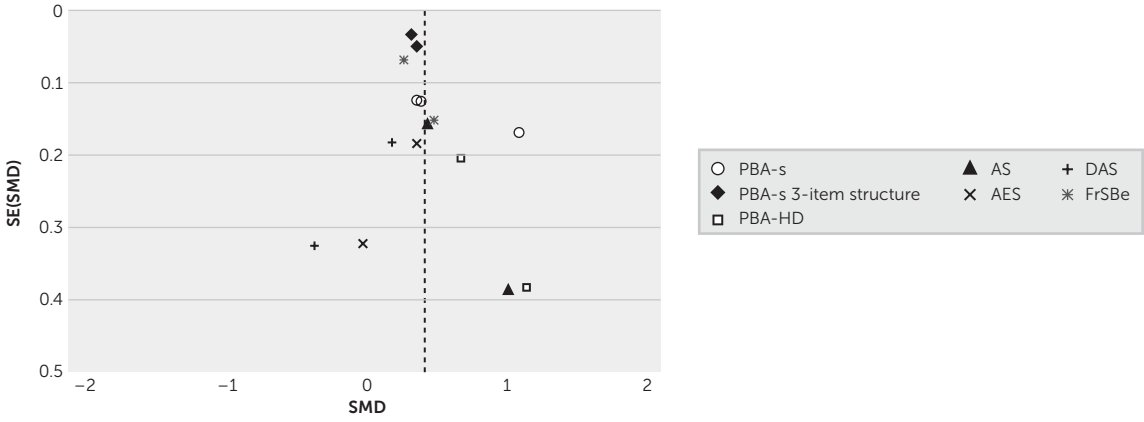
FIGURE 2. Apathy scores in patients with premanifest Huntington disease versus control individuals[a]

Study or Subgroup	Premanifest HD Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.1.1 PBA-s								
Martinez-Horta 2016	2.56	3.56	59	0.1	0.9	101	6.3%	1.08 (0.73, 1.42)
Read 2013	1.14	2.56	118	0.36	1.31	120	8.2%	0.38 (0.13, 0.64)
Tabrizi 2009	1.09	2.56	120	0.38	1.27	123	8.3%	0.35 (0.10, 0.61)
Subtotal (95% CI)			**297**			**344**	**22.8%**	**0.59 (0.18, 1.00)**
Heterogeneity: τ^2=0.11; χ^2=12.95, df=2 (p=0.002); I^2=85%								
Test for overall effect: Z=2.79 (p=0.005)								
2.1.2 PBA-s 3-item structure								
Gunn 2020 P+I	2.23	4.42	641	0.87	2.61	359	11.7%	0.35 (0.22, 0.48)
Gunn 2020 P	1.83	3.86	1149	0.76	2.24	615	12.5%	0.32 (0.22, 0.41)
Subtotal (95% CI)			**1790**			**974**	**24.3%**	**0.33 (0.25, 0.41)**
Heterogeneity: τ^2=0.00; χ^2=0.18, df=1 (p=0.67); I^2=0%								
Test for overall effect: Z=8.21 (p<0.001)								
2.1.3 PBA-HD								
Ceccarini 2019	1.4	2	12	0.1	0.3	27	2.1%	1.14 (0.41, 1.87)
Kingma 2008	1.01	1.86	55	0.11	0.4	56	5.5%	0.67 (0.28, 1.05)
Subtotal (95% CI)			**67**			**83**	**7.7%**	**0.80 (0.38, 1.21)**
Heterogeneity: τ^2=0.02; χ^2=1.25, df=1 (p=0.26); I^2=20%								
Test for overall effect: Z=3.79 (p<0.001)								
2.1.4 AS								
Martinez-Horta 2020a	5.2	7	16	0.1	0.3	16	2.1%	1.00 (0.26, 1.74)
McColgan 2017	11.4	7	92	8.8	4.8	94	7.4%	0.43 (0.14, 0.72)
Subtotal (95% CI)			**108**			**110**	**9.5%**	**0.61 (0.09, 1.13)**
Heterogeneity: τ^2=0.08; χ^2=1.98, df=1 (p=0.16); I^2=49%								
Test for overall effect: Z=2.31 (p=0.02)								
2.1.5 AES								
Atkins 2020	27.4	5.7	20	27.6	6.4	20	2.8%	−0.03 (−0.65, 0.59)
Atkins 2021	30.96	9.24	50	28.28	6.55	87	6.1%	0.35 (−0.00, 0.70)
Subtotal (95% CI)			**70**			**107**	**8.9%**	**0.25 (−0.08, 0.58)**
Heterogeneity: τ^2=0.01; χ^2=1.10, df=1 (p=0.29); I^2=9%								
Test for overall effect: Z=1.47 (p=0.14)								
2.1.6 DAS								
Atkins 2020	19.7	8.3	20	22.6	6.7	20	2.8%	−0.38 (−1.00, 0.25)
Atkins 2021	24.18	10.85	50	22.66	6.98	87	6.1%	0.18 (−0.17, 0.52)
Subtotal (95% CI)			**70**			**107**	**8.9%**	**−0.04 (−0.56, 0.49)**
Heterogeneity: τ^2=0.09; χ^2=2.29, df=1 (p=0.13); I^2=56%								
Test for overall effect: Z=0.14 (p=0.89)								
2.1.7 FrSBe								
Andrews 2018	27.6	8.13	60	24.23	6.47	119	6.9%	0.47 (0.16, 0.79)
Misiura 2019	12.4	5.54	797	11	4.29	208	11.1%	0.26 (0.11, 0.42)
Subtotal (95% CI)			**857**			**327**	**18.0%**	**0.32 (0.14, 0.51)**
Heterogeneity: τ^2=0.01; χ^2=1.40, df=1 (p=0.24); I^2=29%								
Test for overall effect: Z=3.40 (p<0.001)								
Total (95% CI)			**3259**			**2052**	**100.0%**	**0.41 (0.29, 0.52)**
Heterogeneity: τ^2=0.03; χ^2=37.59, df=14 (p<0.001); I^2=63%								
Test for overall effect: Z=6.85 (p<0.001)								
Test for subgroup differences: χ^2=9.53, df=6 (p=0.15); I^2=37.0%								

Std. Mean Difference IV, Random, 95% CI

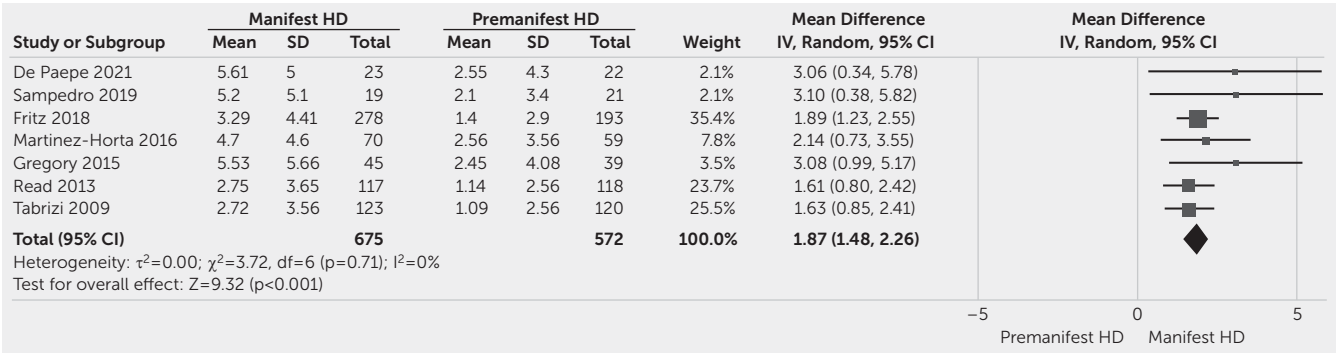
−2 −1 0 1 2

Control Premanifest HD



[a] AES=Apathy Evaluation Scale; AS=Apathy Scale; DAS=Dimensional Apathy Scale; FrSBe=Frontal Systems Behavior Scale; PBA-s=Problem Behaviors Assessment–Short.

FIGURE 3. Apathy scores in patients with premanifest Huntington disease (HD) versus patients with manifest HD



cognitive decline (75). Van Duijn et al. (36) reported lower global cognitive function, as evaluated by the Mini-Mental State Examination (MMSE), and lower executive cognitive function in HD patients with apathy than in those without apathy. Reedeker et al. (34) showed that MMSE scores were the main predictor of apathy. Martinez-Horta and colleagues found strong correlations between apathy and all measures of the UHDRS cognitive score (86), and a moderate correlation between apathy and MMSE scores (79). In a study by Fritz et al. (84), although there was no association with clinician-rated cognition scores (Stroop test, Symbol Digit Modalities Test, and verbal fluency), apathy was significantly correlated with self-rated cognition measures, suggesting that apathy has a more severe effect on functional capacity and independence than objective cognition measures. In contrast, McAllister et al. (103) found that Symbol Digit Modalities Test and Stroop test scores were significantly correlated with apathy. In a study by Baudic et al. (21), HD patients with apathy showed significant deficits in global cognition (assessed by the Mattis Dementia Rating Scale), attention and executive function, and episodic memory, but they showed no significant differences in language and visuospatial task performance.

Social cognition. In a study with patients with premanifest HD and apathy, Martinez-Horta et al. (29) demonstrated a significant decrease in the N170 component, which is a face-sensitive event-related brain potential. Interestingly, this deficit can be present for more than 15 years before the estimated time of disease onset (29). Using the awareness of social inference test, Osborne-Crowley et al. (81) and Kempnich et al. (46) showed decreased facial expression recognition among HD patients with apathy. In summary, there is evidence of decreased facial expression recognition among HD patients with apathy.

Irritability. Bouwens et al. (32) reported a correlation between apathy and irritability over a 2-year follow-up period. However, Burns et al. (20) reported no correlation between measures of apathy, irritability, and aggression in HD patients. Similarly, Martinez-Horta et al. (73) did not find significant difference in apathy frequency when comparing two groups of HD patients with and without irritability or aggression.

Depression. Several studies have shown an overlap between apathy and depression (21, 26, 36, 44, 45, 59, 77, 88). The seminal study by Levy et al. (4) involving patients with different neurodegenerative diseases showed that patients can have apathy without depression and vice versa. Similarly, Naarding et al. (27) found no association between apathy and depression in a small series of HD patients. De Paepe et al. (74) examined gray matter volume changes in HD patients to map apathy circuits and showed that UHDRS cognition scores were associated with apathy but not depression. Isaacs et al. (43) evaluated the performance of apathy scales (PBA-s and FrSBe) versus formal psychiatric assessment by a psychiatrist with HD experience. The PBA-s and psychiatric assessments were comparable in detection of depression but not apathy. On the other hand, the FrSBe detected apathy in accordance with psychiatric assessment (43).

Motor functioning. Higher apathy scores were related to worse motor function, as generally assessed by the UHDRS total motor score (TMS) (25, 26, 28, 36, 46, 47, 59, 70, 77, 81, 86). Thompson et al. (70) evaluated three behavioral changes in HD patients (apathy, depression, and irritability) and found that motor symptoms were correlated only with apathy. Sousa et al. (25) reported that the TMS was the only factor that could independently predict apathy. Andrews et al. (77) reported that apathy scores were correlated with TMS in early HD patients. Conversely, a few studies did not find any correlation between apathy and motor scores (67, 80, 103). Van Duijn et al. (67) did not detect any significant change in PBA apathy scores or any correlation between apathy and the TMS. McAllister et al. (103) found no significant correlation between apathy and the TMS after reviewing the records of 6,316 individuals from the REGISTRY data.

Functional abilities. Functional capacity and related independence scales are global measures of disability in activities of daily living. These measures indirectly assess related functions, such as overall motor disability and cognitive impairment (70). The functional domain of the UHDRS includes three components: TFC scale, functional assessment

scale, and independence scale (IS) (64). The TFC scale has been widely used as a measure of clinical severity in HD (106). Several studies have reported a strong inverse association between TFC and apathy (2, 12, 27, 34, 36, 43, 50, 59, 70, 80, 86–88, 103). In a 36-month study, Tabrizi et al. (13) found this correlation only in patients with early manifest HD, not in patients with premanifest or late manifest HD. Two studies investigated employment as a measure of functional capacity. Jacobs et al. (85) identified cognitive impairment and apathy as two independent predictors of unemployment in a mixed population of patients with manifest and premanifest HD. Van der Zwaan et al. (10) performed an analysis on a sample of 2,791 individuals included in the Enroll-HD database and found that apathy was the most important factor of working capacity reduction among patients with premanifest HD. However, in patients with manifest HD, executive and motor dysfunction had a greater influence on the reduction in working capacity (10).

Pathophysiology of Apathy in HD Patients

The pathophysiology of HD has been classically linked to basal ganglia dysfunction. The striatum is one of the first brain regions affected by the HD-related neurodegenerative process. With disease progression, gray matter loss becomes evident beyond the striatum, affecting various cortical regions. White matter loss has also been reported in early stages with loss of functional connectivity in patients with premanifest HD (95).

Fourteen studies investigated the pathophysiology of apathy in HD patients (28–30, 44, 65, 74, 80, 82, 83, 86, 89, 90, 92, 95). Here, we discuss the most prominent findings.

Cingulate cortex. The cingulate cortex has three main parts: anterior cingulate cortex (ACC), midcingulate cortex (MCC), and posterior cingulate cortex (PCC). The ACC is a processing center for autonomic function and emotional responses. The MCC is responsible for various aspects of cognitive control such as response selection, attention-related processing, and error detection. The PCC is a functionally heterogeneous region with high metabolic activity and dense connections to other brain regions (107–109).

Studies on normal motivated behavior have shown a strong correlation between aspects of the ACC and apathy (110). Decreased metabolic activity, as assessed by fluorodeoxyglucose positron emission tomography (PET), has been detected in the dorsal ACC in HD patients with apathy (86). De Paepe et al. (74) found atrophy of the MCC, not the ACC, on MRI in HD patients with apathy.

Other cortical regions. Findings of PET studies in HD patients have shown significant decreases in metabolism in the prefrontal cortex (PFC) and its targets, including the ACC (86). In addition, the involvement of other cortical areas such as frontotemporal, parietal, insular, and occipital cortices have also been observed (82, 86). Martinez-Horta et al. (29) showed that visuoperceptual deficits (i.e., disruption of face-like object recognition) were associated with the severity of apathy in patients with premanifest HD, possibly resulting from impairments in the fusiform gyrus.

Basal ganglia, thalamus, and limbic system. Degeneration of the striatum is a prominent feature of HD. Martinez-Horta et al. (86) provided evidence in favor of the hypothesis of a role for basal ganglia degeneration in apathy development by demonstrating atrophy of various gray matter regions, including the striatum, in HD patients with apathy. They also showed that a complex cortico-subcortical emotion-related network, which includes the hippocampus and amygdala, is affected in those with apathy (86). Misiura et al. (44) reported significant relationships between apathy and atrophy of the putamen and caudate but not the thalamus. In contrast, Baake et al. (83) showed a correlation between apathy and atrophy of the thalamus at baseline but no significant relationship between apathy and volume change of subcortical structures over a 2-year follow-up.

White matter. MRI with diffusion tensor imaging (DTI) was used in four studies to detect white matter correlates of apathy in HD patients, and the results were inconsistent (30, 80, 89, 90). One study reported changes in the rectus gyrus, and two other studies found no significant correlation between apathy and white matter change (30, 89, 90). In an attempt to reduce the effect of heterogeneity on DTI measures, De Paepe et al. (80) considered apathy subtypes (cognitive, emotional, and autoactivation) in their analysis. They found correlations between different apathy profiles and white matter tracts, including the frontostriatal tract, which connects the presupplementary motor areas to the caudate nucleus (cognitive subtype); uncinate fasciculus, which connects the anterior temporal lobe to the amygdala and orbitofrontal cortex (autoactivation subtype); and dorsolateral PFC to caudate nucleus tract (cognitive subtype) (80).

A few studies also evaluated functional connectivity (28, 30). Nair et al. (28) used resting-state functional MRI data to model dysfunction of the direct and indirect pathways in patients with premanifest HD. Apathy was associated with dysfunction of the striatothalamic (direct pathway) connectivity (28).

Blood Markers Correlated With Apathy in HD Patients

The potential association of blood markers with apathy in HD was investigated in two studies by Bouwens et al. (31, 66). In the first study (66), they examined concentrations of C-reactive protein (CRP) and albumin and reported significant associations between CRP and several factors, including apathy, TFC, and cognitive impairment. However, the association disappeared after adjusting the multilevel regression model for antipsychotic use (66). Their second study (31) evaluated plasma levels of cytokines, including TNF-α, interleukin (IL)-1ra, IL-1, IL-5, IL-6, IL-8, and IL-10. Only cognitive dysfunction was weakly associated with IL-1ra and

IL-6. Other neuropsychiatric symptoms, including apathy, showed no associations with cytokine levels (31).

DISCUSSION

Apathy is a common neuropsychiatric symptom of HD and is associated with disease progression. Our meta-analysis revealed higher apathy scores in patients with manifest HD than in patients with premanifest HD. The heterogeneous data showed that patients with premanifest HD had higher apathy scores than healthy control individuals. The frequency of apathy generally ranged from 10% to 33% among patients with premanifest HD and from 24% to 76% among patients with manifest HD. The numbers varied significantly among studies, reflecting methodological differences (e.g., case definition, assessment tools, source of information, definition of premanifest and manifest HD subcategories) and characteristics of the sample studied, with more advanced HD leading to higher frequency and severity of apathy.

Several instruments have been used to investigate apathy in HD patients. The PBA-s was the most commonly used instrument due to its specific validation in HD and sensitivity to change over the course of the disease (96). Other apathy scoring tools, such as the AES, AS, and FrSBe (apathy subscale), have not undergone proper validation, specifically within HD patient populations. In the best-case scenario, the validity was assessed in a patient population with a variety of neurodegenerative diseases (111). Furthermore, differences in the suggested cutoff scores hampered the process of defining a more reliable picture of HD-related apathy. For the PBA-s, for instance, the cutoff scores were defined as severity score of $\geq$1, $\geq$2, or $>$2 in different studies. The reporting of apathy severity was also inconsistent among the studies. PBA and PBA-s scores have been reported in different ways; for example, studies have reported PBA-s apathy severity scores only (range: 0–4), the product of apathy severity and frequency scores (range: 0–16), the PBA-s three-item structure (apathy, perseveration, and disorientation; range: 0–48), the PBA-HD four-item factor (lack of perseverance, poor quality of work, lack of initiative, and poor self-care; range: 0–64), or the original PBA-HD factor with seven items (range: 0–16).

To overcome these shortcomings, consensus-based diagnostic criteria for apathy were proposed (7). Although these criteria do not measure apathy severity, they provide a diagnostic structure and thus a more reliable case definition. Four criteria should be met for a diagnosis of apathy: a quantitative reduction in goal-directed activity in comparison to the patient's previous levels of functioning, symptoms and duration, exclusionary criteria, and severity. Three dimensions were defined for symptoms: behavior and cognition, emotion, and social interaction. The patient should have at least one symptom in at least two dimensions, and the symptoms should be persistent or frequently recur over at least 4 weeks (6, 7). The applicability of these diagnostic criteria in HD needs to be investigated as well as their interaction with clinical tools. Illustrating the relevance of this latter point, the PBA-s and FrSBe had divergent performances compared to formal psychiatric assessments to identify cases of apathy in HD (43). Therefore, additional studies are needed to establish gold-standard criteria and scales for the assessment of apathy in HD patients.

In this review, we excluded studies that did not use a dedicated apathy scale or subscale. For instance, the BDI assesses loss of interest as a part of depression and does not assess apathy as a discrete entity. While disorders of motivation, including apathy and anhedonia, are relevant elements of depression, they are neither necessary nor sufficient to define the depressive syndrome. Conversely, it is recognized that there is a clinical overlap between apathy and depression (7, 27). Since depressed mood is one of the early symptoms of HD and given the therapeutic implications, differentiating depressed mood from apathy is clinically relevant (7, 67). A better understanding of the overlapping versus divergent trajectories of these two neurobehavioral syndromes is definitely warranted in HD.

Apathy was associated with cognitive decline, affecting both global cognition and executive function. Of note, an inability to program and execute plans—core features of executive function—can result in reduced goal-directed behaviors, a subdomain of apathy, indicating a close link between these two constructs (21). Associations between apathy and cognitive decline have also been shown in other neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD) (112, 113). Even among cognitively normal individuals, apathy was associated with a twofold increase in the risk of conversion to mild cognitive impairment (114). Taken together, these findings underscore the importance of apathy as a proxy for cognitive decline.

The association of apathy with irritability in HD can be explained by the involvement of relevant subcortical and frontal circuits. Only one study provided evidence in support of the connection between apathy and irritability (32). It has been suggested that apathy may mask irritability, resulting in the lack of overt external expression of anger (32). As anosognosia frequently occurs in HD patients, detection of irritability can be challenging in HD patients with apathy and requires a detailed interview with the patient and caregiver.

A role for a number of brain structures has been consistently reported across different disorders associated with apathy, especially PD and AD; these structures include the ventral tegmental area of the midbrain, ventral striatum, and various parts of the PFC, including the ACC (110, 115). There are fewer neuroimaging studies evaluating apathy in neurodegenerative diseases such as frontotemporal dementia, progressive supranuclear palsy, and HD than in PD and AD (115). Although the involvement of structures related to effort-based decision making seems to be a common feature of apathy across all these diseases, further studies are required to define the neural basis and pathophysiology of apathy in HD patients.

Our findings should be interpreted in the context of three main limitations. First, the data involved in the comparisons between patients with premanifest HD and control individuals were very heterogeneous. Second, due to the lack of consensus cutoff scores for apathy scales, we used only apathy scores, not the number of patients with apathy, for the meta-analysis. Third, investigating the potential associations between apathy and other clinical domains (e.g., cognition and social functioning) can be affected by confounding factors that were not well controlled in several studies during their design (e.g., randomization) and analysis (e.g., multivariate strategies).

CONCLUSIONS

In our review, apathy was more frequently observed in individuals with premanifest HD than those in a control group and in manifest versus premanifest HD. Despite the heterogeneity of the data, apathy appears to have a progressive nature in HD. The correlation between apathy and cognitive decline highlights the importance of apathy as a neurobehavioral symptom. Thus, apathy should be closely monitored throughout the disease course and may be considered a clinical surrogate biomarker for disease progression. Considering the complexity of apathy and its unique pattern of development in neurodegenerative diseases, further studies are required to explore its pathophysiology in HD.

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