Understanding the Relationship Between Perseveration, Comorbid Behavioral Symptoms, Motor Decline, Functional Decline, and Self-report Accuracy in Huntington Disease Can Help Inform Clinical Practice

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Background: Perseveration is one of the most debilitating symptoms of Huntington disease (HD).

Objective: To study perseveration and its relationship to comorbid behavioral symptoms, motor decline, functional decline, and subject self-report accuracy by analyzing cross-sectional data tracking individuals who have or are at risk for HD and healthy controls (HC).

Method: We studied 96 individuals from HD families and 35 HC who were either family controls or gene negative. We used χ^2 tests to compare patient demographic and survey outcomes data and to analyze the presence of obsessions and compulsions (OC), depression, and apathy relative to the presence of perseveration.

Results: Individuals with HD and perseveration had a higher presence of OC, depression, and apathy compared with individuals with HD of the same stages without perseveration (19%, 47.6%, and 47.6% vs 15%, 40%, and 25%, respectively). In addition, individuals in HD Stages 1–3 with higher motor scores (showing a later stage of disease) displayed a significantly higher rate of perseveration than the HC ($P = 0.0476$; $P = 0.0499$, respectively). The presence of an informant resulted in a significantly higher rate of perseveration reporting for individuals in HD Stages 1 and 2 (41.2% and 53.8% with informant vs 23.5% and 11.1% without informant, respectively).

Conclusion: Perseveration was seen across all motor and functional stages for the individuals with HD, without significant differences between the different stages. Additionally, informants were beneficial to obtaining accurate patient reports of perseveration. These findings should prove useful for physician evaluation and treatment considerations.

Key Words: Huntington disease, perseveration, obsessions, compulsions

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CAG = cytosine-adenine-guanine. **HC** = healthy controls. **HD** = Huntington disease. **OC** = obsessions and compulsions. **PBA–s** = Problem Behaviours Assessment—Short Form. **TFC** = Total Functional Capacity. **TMS** = Total Motor score.

Huntington disease (HD) is an autosomal-dominant neurodegenerative disease with behavioral, motor, and cognitive symptoms. Individuals with HD often exhibit comorbid behavioral symptoms such as perseveration, anxiety, depression, disinhibition, irritability, apathy, and psychosis, as well as impaired social cognition (Cummings and Cunningham, 1992; Lichter and Cummings, 2000; Modell et al, 1989; Patzold and Brüne, 2002). Of the behavioral comorbidities in HD, perseveration is one of the most debilitating.

Perseveration is a behavioral symptom that is present in a variety of diseases, from HD to schizophrenia and Alzheimer disease (Sandson and Albert, 1984). Perseveration is characterized by repeatedly producing a particular action or thought and can be the result of inhibitory deficits (Hauser, 1999). With a similar clinical manifestation, and often not distinguished from perseveration by clinicians, *obsessions and compulsions* (OC) are one of the most common behavioral symptoms in individuals with HD (American Psychiatric Association, 2013).

In addition to OC, apathy and depression are commonly exhibited by individuals with HD (Huntington Study Group, 1996). *Apathy* is the lack of motivation or lack of responsiveness to stimuli; *depression* is sadness or a depressed mood over an extended time period (Mayberg et al, 1992; Van Reekum et al, 2005). Dysfunction of the frontal cortex and basal ganglia is common to all four behavioral symptoms.

Our objective was to study perseveration and other comorbid behavioral symptoms (eg, OC, apathy, depression) in individuals with HD, as well as perseveration's relationship to motor and functional decline. We examined three groups—individuals with HD, at-risk family members of individuals with HD, and healthy controls (HC; non–cytosine-adenine-guanine [CAG] expansion mutation carriers)—from the Enroll-HD database (2020), which is a worldwide, observational clinical study of individuals with

HD. By understanding the relationship between perseveration and comorbid behavioral symptoms, motor decline, functional decline, and subject self-report accuracy in individuals with HD, we can better elucidate the pathophysiology of HD as well as inform best practices for patient interviewing in clinical settings.

Currently, it is unclear what the relationship is between perseveration and disease severity in individuals with HD. Some researchers have suggested that perseveration is related to the specific stage of HD (De Lucia et al, 2020); others have suggested that perseveration is related to the progressive impairment of attention and working memory (Kramer et al, 1988; Rich et al, 1997).

We hypothesized that individuals with HD who exhibit OC, apathy, and/or depression would be likely to exhibit perseveration. We also hypothesized that the rate of perseveration would increase in relation to motor and functional decline in individuals with HD. Finally, we hypothesized that informants would report perseveration in individuals with HD at significantly higher rates than the individuals themselves. Individuals with HD lack insight into the presence of their own symptoms (Sitek et al, 2014); thus, we expected to see more perseveration in individuals whose surveys were completed by an informant.

METHOD

Participants

We collected data from individuals who were in the Enroll-HD database. In order to be included in our study, individuals had to have one or more of the following scores: Total Functional Capacity (TFC) Scale (Huntington Study Group, 1996) score, Unified Huntington's Disease Rating Scale (Huntington Study Group, 1996) Total Motor score (TMS), or Problem Behaviours Assessment—Short Form (PBA–s) score (Callaghan et al, 2015).

In addition, individuals had to be age ≥18 years and qualify as either (a) gene negative, (b) asymptomatic gene positive, or (c) symptomatic gene positive. We separated the individuals into a control group and an experimental group. We placed the gene-negative individuals into the control group and both the asymptomatic and the symptomatic gene-positive individuals into the experimental group. We used the TMS to rate the severity of each individual's HD symptoms.

The study protocol was approved by the institutional review board of the Georgetown Medical School in Washington, DC, and was performed according to the ethical guidelines of the Declaration of Helsinki and its later amendments. All individuals provided informed written consent before enrolling in the study.

Measures

CAG Repeat Length

We used CAG repeat length to assess each individual's gene status. A CAG repeat length ≥35 indicates a gene-positive individual; a CAG repeat length <35 indicates a gene-negative individual. Above the cutoff, there is a range of possible expansions that may differ for each individual.

TFC Scale Score

We used the TFC Scale to assess each individual's daily functional ability. The score ranges from 0 to 13 points, with higher scores representing better functional capacity. We interpreted the TFC Scale scores according to the previously established cutoffs: A score of 11–13 = HD Stage 1, 7–10 = HD Stage 2, and 3–6 = HD Stage 3 (Huntington Study Group, 1996). The TFC Scale includes Stages 4 and 5, but no one in our sample received those scores.

Perseveration, OC, Apathy, and Depression

We used the PBA–s, a series of semistructured interview questions, to assess the presence of behavioral symptoms (ie, perseveration, OC, apathy, and depression). The assessment contains 11 questions (McNally et al, 2015). Question 7 asks if, in the past 4 weeks, the individual or his or her family members found themselves getting stuck on certain thoughts or actions. We used this question to assess for the presence of perseveration. We used PBA–s questions 8, 6, and 1 to assess for the presence of OC, apathy, and depression, respectively.

PBA–s questions capture both the frequency and the severity of designated symptoms on a scale of 0 to 4, with 0 indicating no symptoms present (no frequency and no severity). A score of ≥2 on the severity scale was used to indicate the presence of a symptom. Prior work has used this methodology (Callaghan et al, 2015).

Total Motor Score

We used the Unified Huntington's Disease Rating Scale to assess the severity of each individual's HD symptoms (eg, chorea, dystonia, eye movement, coordination, balance, and gait). The TMS is based on 31 questions. Each question has a possible score of 0 to 4, with 0 indicating normal function. The TMS is the sum of all 31 scores (Huntington Study Group, 1996).

Statistical Analysis

Demographic Analysis

We separated the experimental group into two subgroups—individuals with perseveration and individuals without perseveration—and compared them for sex; race; age; CAG repeat length; CAG Age Product score, which is an objective measure of disease burden based on age, CAG, and correction factor; TFC Scale score; TMS; antidepressant use; and antipsychotic use (Ross et al, 2014).

We analyzed the presence of perseveration in relation to motor and functional symptoms to help elucidate the pathophysiological changes leading to behavioral symptoms in individuals with HD. Statistical analysis was conducted, and P values < 0.05 were taken to indicate statistical significance. The presence of comorbid behavioral symptoms in the perseverative subgroup versus the nonperseverative subgroup, as well as the presence of perseveration with disease stage, were the main comparisons of interest. We used the Kruskal Wallis test to compare

individual demographic and survey outcomes data in Microsoft Excel.

Perseveration in Relation to Comorbid Behavioral Symptoms

We divided the experimental group into stages of HD based on their TFC Scale scores. Next, we separated the perseverative subgroup into HD Stages 1–3 and analyzed them by stage for the presence of OC, apathy, and depression. We defined the presence of perseveration as any individual reporting ≥2 on PBA–s question 7. We also separated the nonperseverative subgroup into HD Stages 1–3 and analyzed them by stage for the presence of OC, apathy, and depression. The rate of comorbid symptoms in the nonperseverative subgroup served as the expected rate of comorbid symptoms. We then compared the rates of each symptom of the individuals in the perseverative subgroup with the expected rates of each symptom.

Perseveration in Relation to Motor Decline

To analyze the TMS relative to the frequency of perseveration, we divided the experimental group into three subgroups of approximately equal numbers: Motor A (TMS = 2–15), Motor B (TMS = 16–33), and Motor C (TMS = 34–63). This separation into subgroups was an exploratory measure to incorporate motor disability analysis—the main physical manifestation of HD—because there is no current established staging for the TMS. A Kruskal Wallis test determined the significance of the difference in proportions of symptoms to nonsymptoms in each TMS category.

Perseveration in Relation to Functional Decline

The rate of perseveration from the control group served as the benchmark expected rate for the three HD stages. Next, we used the Kruskal Wallis test to compare the actual rate observed in each stage to the expected control rate. We also used the Kruskal Wallis test to compare the rates of perseveration among the HD stages.

Perseveration in Relation to the Presence of an Informant

We analyzed the individuals with HD Stages 1 and 2 to see whether the presence of an informant had any effect on their reported rates of perseveration. HD Stage 3 was not included in the analysis because all of the individuals in Stage 3 had an informant, thus rendering this analysis impossible. A χ^2 test was used to determine the significance of the difference between the reported rates of perseveration.

RESULTS

Participants

We identified 148 individuals age ≥18 years from the Enroll-HD database who were either (a) gene negative, (b) asymptomatic gene positive, or (c) symptomatic gene positive. We excluded 44 individuals for an incomplete TFC Scale score, TMS, or PBA–s score. Eight individuals were also excluded for missing genotype data.

We separated the remaining 96 individuals into the control and experimental groups. Gene-negative individuals were placed in the control group (n = 35); gene-positive asymptomatic individuals (n = 4) and gene-positive symptomatic individuals (n = 57) with gene expansion mutations were placed in the experimental group (Table 1).

There were slightly more females than males in both the control (53% female) and experimental groups (52% female). The vast majority of the individuals were Caucasian (control = 91.2%, experimental = 98.4%), with a small number of Black, East Asian, and others. Compared with the control group, the experimental group had a significantly lower mean age (53.4 < 59.8), mean TFC Scale score (9.8 < 13), and rate of marriage (45.9% < 75.8%), along with a significantly higher mean TMS (30.6 > 3.9) and rate of antipsychotic use (11.5% > 0%), as well as an increased rate of antidepressant use (44.3% > 24.2%).

Our experimental group represented a wide spectrum of disease stages, with TMSs ranging from 2 to 63 and HD stages ranging from 1 to 3. Thirty of the individuals in the experimental group brought an optional informant who helped report on their behavioral symptoms.

Perseveration in Relation to Comorbid Behavioral Symptoms

We found an increased rate of perseveration with the presence of OC, depression, and apathy (Table 2, $P > 0.05$). The perseverative and nonperseverative

TABLE 1. Demographic Comparison of the Gene-negative (Control) Group and the Gene-positive (Experimental) Group

Characteristic/Score	HC (n = 33)†	HD (n = 61)	*P*
Sex (% female)	53	52	0.93
Race (% Caucasian)	91.2	98.4	0.10
Age (years)	59.8 ± 13.3	53.4 ± 12.4	0.02*
CAG repeat length	NA	42.1 ± 2.5	NA
CAP score	NA	101.8 ± 26.9	NA
TFC Scale score	13 ± 0	9.8 ± 3.3	0.0001*
TMS	3.9 ± 4.5	30.6 ± 16.4	0.00001***
Married (%)	75.8	45.9	0.01*
Use alcohol (%)	69.7	54.1	0.14
Smoker (%)	12.1	13.1	0.89
Antidepressant use (%)‡	24.2	44.3	0.06
Antipsychotic use (%)§	0	11.5	0.04*

Values are presented as M ± SD unless noted otherwise.
*Significant at $P < 0.05$.
***Significant at $P < 0.001$.
†Two individuals were excluded for incomplete data.
‡Citalopram, duloxetine, doxepin, fluvoxamine, escitalopram, paroxetine, fluoxetine, mirtazapine, sertraline, venlafaxine, bupropion.
§Aripiprazole, olanzapine, and quetiapine.
CAG = cytosine-adenine-guanine. **CAP** = CAG Age Product. **HC** = healthy controls. **HD** = Huntington disease. **NA** = not applicable. **TFC** = Total Functional Capacity. **TMS** = Total Motor score.

TABLE 2. Incidence of OC, Depression, and Apathy in the Perseverative Subgroup Versus the Nonperseverative Subgroup ($P > 0.05$)

	HD Stage 1	HD Stage 2	HD Stage 3	Overall	Statistics
Individuals with perseveration	11	8	2	21	
Observed OC (%)	18.2	25	0	19	OCs $\chi^2_{(2,\ n\ =\ 19)} = 0.194$, $P = 0.659$
Expected OC (%)	13	21.4	0	15	
Observed depression (%)	63.6	30	0	47.6	Depression $\chi^2_{(2,\ n\ =\ 19)} = 1.90$, $P = 0.168$
Expected depression (%)	30.4	57.1	33.3	40	
Observed apathy (%)	63.6	37.5	0	47.6	Apathy $\chi^2_{(2,\ n\ =\ 19)} = 0.15$, $P = 0.699$
Expected apathy (%)	26.1	28.6	0	25	

Expected = rate of symptom in nonperseverative subjects of the same stage. **HD** = Huntington disease. **OC** = obsessions and compulsions.

subgroups did not differ significantly in any other category (Table 3).

Perseveration in Relation to Motor Decline

In our experimental group, 30%, 33.3%, and 35% of the individuals in Motor groups A, B, and C, respectively, reported perseveration. The rate of perseveration among the control group was 5.7%. All of the motor subgroups had significantly higher rates of perseveration compared with the control group (H [N = 96] = 8.08, $P = 0.04436 < 0.05$). There were no significant differences in perseveration rates among the three motor subgroups ($P > 0.05$) (Figure 1).

Perseveration in Relation to Functional Decline

In our functional analysis, the percentage of individuals displaying perseveration in the control group was used as the standard in the population of those without HD (n = 35, 5.71%). The percentage of individuals in the HD subgroups showing symptoms of perseveration in HD Stage 1 (n = 34), Stage 2 (n = 22), and Stage 3 (n = 5) were 32.4%, 36.4%, and 40%, respectively. All of the HD stage subgroups had significantly higher rates of perseveration compared with the control group (H [N = 96] = 8.82, $P = 0.0499 < 0.05$). There were no significant differences in perseveration rates among the three stage subgroups ($P > 0.05$) (Figure 2).

Perseveration in Relation to the Presence of an Informant

Subsequently, we looked for factors that may have affected the individuals' reports of behavioral symptoms. Individuals from HD Stages 1 and 2, as distinguished by the TFC Scale score, were separated into those who had an informant present (n = 30) and those who did not (n = 26). The informants reported increased rates of patient perseveration compared with the individuals

TABLE 3. Demographic Comparison of Gene-positive Subgroup With Perseveration and Gene-positive Subgroup Without Perseveration

Characteristic	Gene-positive With Perseveration (n = 21, 13†)	Gene-positive Without Perseveration (n = 40, 20†)	*P*
Sex (% female)	43	60	0.35
Race (% Caucasian)	95.2	100	0.33
Age (years)	48.7 ± 12.5	55.0 ± 12.3	0.16
CAG repeat length†	42.7 ± 2.0	41.9 ± 2.8	0.38
CAP score†	97.2 ± 28.7	104.9 ± 25.8	0.43
TFC Scale score	10.2 ± 3.6	10.7 ± 3.0	0.67
TMS (M ± SD)	28.3 ± 19.2	23.2 ± 18.5	0.45
Antidepressant use (%)‡	47.6	42.5	0.78
Antipsychotic use (%)§	19.0	7.5	0.33

Values are presented as M ± SD unless noted otherwise.
All 61 individuals were genotype positive; 4 of the 61 were presymptomatic.
†Only 33 individuals with HD had CAG repeat length data; thus, our comparison for both CAG repeat length and CAP scores are limited to those 33 individuals.
‡Citalopram, duloxetine, doxepin, fluvoxamine, escitalopram, paroxetine, fluoxetine, mirtazapine, sertraline, venlafaxine, bupropion.
§Aripiprazole, olanzapine, quetiapine.
CAG = cytosine-adenine-guanine. **CAP** = CAG Age Product. **TFC** = Total Functional Capacity. **TMS** = Total Motor score.

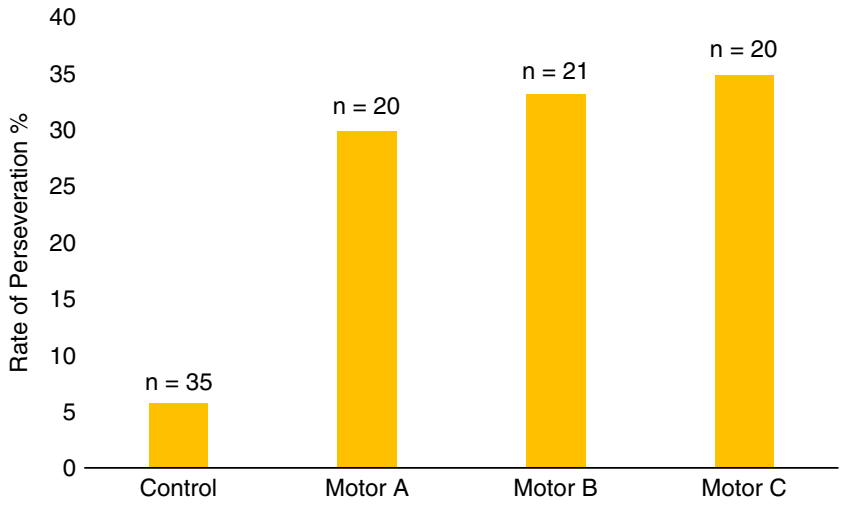

FIGURE 1. Rate of perseveration for the control group compared with the experimental group according to the Total Motor score.

without an informant: HD Stage 1 (41.2% vs 23.5%) and HD Stage 2 (53.8% vs 11.1%) (Figure 3).

DISCUSSION

Our objective was to study the relationship between perseveration and comorbid behavioral symptoms (OC, apathy, and depression), motor and functional decline, and subject self-report accuracy in individuals with HD. We hypothesized that the presence of behavioral symptoms—OC, depression, and apathy—would increase the risk of perseveration, and that informants would report perseveration at higher rates than the individuals themselves. We also hypothesized that gene-positive individuals would be more affected by perseveration than the control group, and that the rate of perseveration would increase with more severe HD.

Our results supported the hypotheses that gene-positive individuals would have an increased presence of perseveration and that informants would report higher rates of perseveration than the individuals themselves. However, our results did not support our hypotheses concerning the relationship between the risk of perseveration and the presence of comorbid behavioral symptoms or the relationship between the risk of perseveration and the severity of HD. These results could be partially explained by the higher rate of antidepressant and antipsychotic use by the experimental

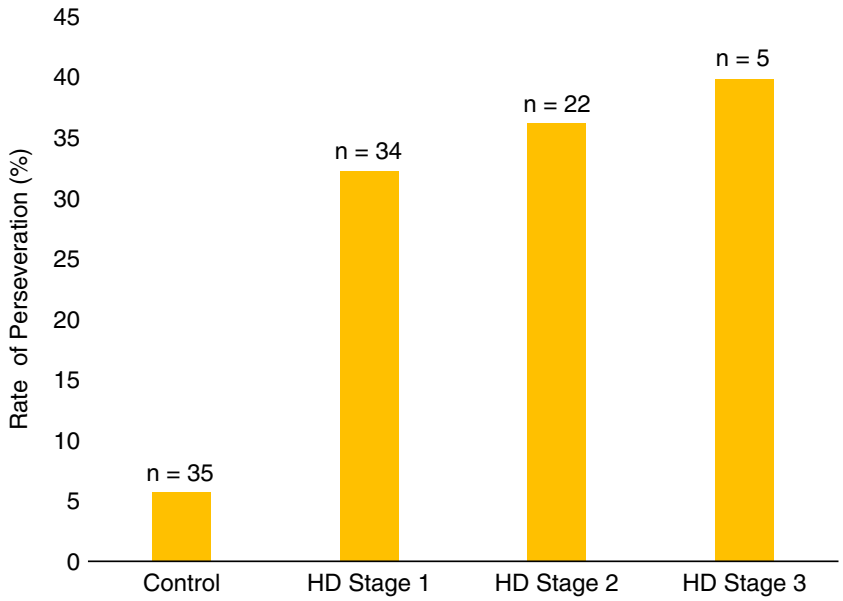

FIGURE 2. Rate of perseveration for the control group compared with the experimental group according to their HD stage. **HD** = Huntington disease.

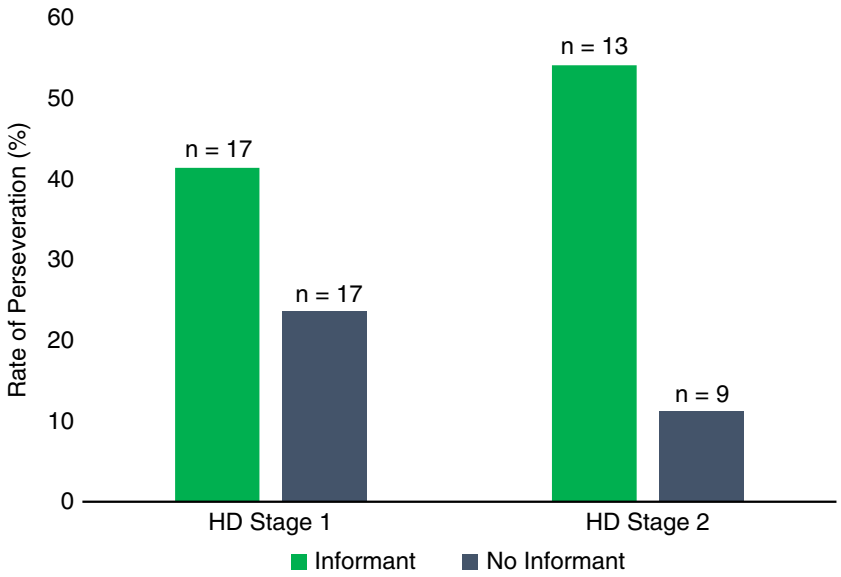

FIGURE 3. Rate of perseveration for individuals with and without an informant. **HD** = Huntington disease. **TFC** = Total Functional Capacity.

group compared with the control group, which could have artificially lowered the observed rates of other behavioral symptoms.

Although both the TMS and the TFC Scale score yielded similar distributions of perseveration per HD stage, we determined that the TFC Scale score is more precise than the TMS in determining disease severity and its correlation to the rate of perseveration because, unlike the TMS, the TFC Scale score has established cutoffs to distinguish between the stages of HD.

Due to the lack of established guidelines for staging HD by the TMS, we chose to analyze our data by dividing the range of motor scores into three subgroups of approximately equal numbers. This lack of guidelines for staging HD by the TMS reflects the idea that HD, although most typically characterized by chorea or dystonia, is perhaps more accurately tracked by its functional effects, which impact one's daily quality of life (Ready et al, 2008).

In general, perseveration is primarily a result of dysfunction in the frontal cortex, whereas motor impairments in individuals with HD are often a result of dysfunction in a different region—the caudate nucleus in the basal ganglia (Cummings and Cunningham, 1992). The TMS, on the other hand, is impacted more by basal ganglia pathology (Alexander et al, 1990), whereas the TFC Scale score is likely impacted more by the motor cortex, superior parietal, and cuneus thinning (Rosas et al, 2008).

We also observed an increased rate of perseveration with the presence of OC, depression, and apathy, but these trends were not significant. Perseveration is primarily associated with frontal lobe damage and posterior left hemisphere damage; damage to the basal ganglia has also been implicated (Sandson and Albert, 1984). Studies have shown that OC, depression, and apathy are associated with dysfunction involving the caudate nucleus and globus pallidus, paralimbic and basal ganglia, and frontal subcortical system, respectively (Cummings and Cunningham, 1992; Mayberg et al, 1992; Van Reekum et al, 2005).

We used the severity scale of the PBA–s to measure the presence or absence of each behavioral symptom because we believe it is more representative of an individual's psychiatric condition, as concluded in McNally et al (2015). Our assessment used question 7 of the PBA–s to detect the rate of perseveration. However, dysfunction of the basal ganglia was common to all four behavioral symptoms that we considered. Therefore, we believe that degeneration of the basal ganglia in individuals with HD exacerbates the risk of perseveration, OC, depression, and apathy, resulting in these comorbidities.

Our data also suggest the utility of informants in clinical settings. Individuals on their own may lack insight or deny symptoms; thus, informants may present a significantly more accurate depiction of an individual's condition. Regarding perseveration, individuals who had an informant scored at more than twice the frequency for perseverative symptoms compared with individuals without an informant. Other work has shown the importance of informants in the study of perseveration (Nordahl et al, 1989).

Study Limitations

Our study faced some limitations. First, our site was not a long-term care facility, thereby skewing our participant population toward individuals with fewer functional impairments than would be found in individuals in a long-term care facility. This type of facility explained our lack of individuals with HD Stage 4 or 5. Additionally, our individuals were seen in a clinical setting and were receiving treatment for their symptoms, making them less affected by HD symptoms than the general population of individuals

with HD. Selective serotonin reuptake inhibitors are commonly used to treat perseveration, OC, and depression; they may worsen apathy (Branford et al, 1998). Given that 47.6% and 42.5% of our gene-positive individuals with and without perseveration, respectively, were taking selective serotonin reuptake inhibitors, the presence and severity of these symptoms may have been reduced.

Future work should include longitudinal studies to explore the potential of OC, depression, and apathy to predict the rate of perseveration. The need to educate families that these behavioral symptoms are a part of HD should be communicated to clinicians. A study involving untreated HD patients as well as multiple types of treatment sites, including long-term care facilities, would help to increase diversity in terms of functional impairment.

CONCLUSION

In our study, perseveration appeared in individuals across Stages 1–3 of HD, whether stage was assessed by motor or functional decline. These findings will help clinicians be more cognizant of the behavioral effects of HD, enabling them to help families understand that perseveration, OC, depression, and apathy are a part of HD. The disparity in individual and informant reports highlights the importance of caregiver assessment in behavioral evaluations for individuals with HD. We hope to draw attention to perseveration, which is one of the lesser known symptoms of HD.

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