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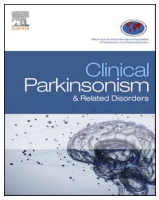

Exploring bradyphrenia in Huntington's disease using the computerized test of information processing (CTiP)

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ABSTRACT

Background: Bradyphrenia, best thought of as the mental equivalent of bradykinesia, has been described in several disorders of the brain including Parkinson's disease and schizophrenia; however, little is known about this phenomenon in Huntington's Disease (HD).
Objective: The aim of this study was to investigate the presence of bradyphrenia in HD using the Computerized Test of Information Processing (CTiP), an easy to administer and objective task that assesses cognitive processing speed with increasing task complexity.
Methods: This study included 211 participants: Huntington's Disease Integrated Staging System (HD-ISS) Stage 0 [n = 28], Stage 1 [n = 30], Stage 2 [n = 48] and Stage 3 [n = 48], and healthy controls (HC) [n = 57]. The CTiP incorporates three subtests: Simple Reaction Time (SRT), which assesses baseline motor function; Choice Reaction Time (CRT), with an added decisional component; and Semantic Search Reaction Time (SSRT), with an added conceptual component. SRT scores were subtracted from CRT and SSRT scores to establish a motor-corrected measure of central conduction time, which was used to operationalize bradyphrenia.
Results: HD-ISS and HC within-group reaction times differed significantly when comparing motor-corrected CRT vs SSRT (all *ps* < 0.0001). Furthermore, the magnitude of these differences increased with HD disease stage ($p < 0.0001$). An ROC analysis determined that motor-corrected within-subject differences significantly distinguished Stage 2 + 3 from Stage 0 + 1 (AUC = 0.72, $p < 0.0001$).
Conclusions: We report evidence of bradyphrenia in HD that increases with disease progression. This processing deficit, which can be quantified using the CTiP, has the potential to greatly impact HD daily life and warrants additional research.

1. Introduction

Bradyphrenia, best thought of as the mental equivalent of bradykinesia, is the slowing of cognitive processing with increasing task complexity. The term bradyphrenia, originating from ancient Greek meaning 'slow mind', was first documented in 1922 by neurologist Naville to describe a phenotypic presentation most frequently observed as part of the encephalitis lethargica epidemic of the time [1,2]. Following this, Steck (1931) assessed post-encephalitic mental syndromes across 27 institutions in Switzerland, including participants involved in Naville's study, and found that the predominanting two symptoms were personality change and bradyphrenia. Steck also contributed to the definition of this disorder, describing bradyphrenia symptomatology as exclusive from disturbances in memory, judgement and orientation [1,3]. In 1953, Hassler redefined bradyphrenia as psychic akinesia, relating it to cell loss in the basal ganglia [1]. More recently, bradyphrenia has been documented in Parkinson's disease (PD), as well as lewy body dementia [1,4]. Outside the scope of dementia, bradyphrenia has also been reported in schizophrenia, as measured by an increased frequency and duration of pauses in free-speech, but not motoric only rote-speech [5]. A separate study described bradyphrenia, as measured by a significant diagnosis x item complexity interaction effect using a modified version of the Tower of London test, in PD and Huntington's disease (HD), but not schizophrenia [6]. This latter preliminary study by Hanes and colleagues, conducted in 1996, is notably the only quantitative assessment of bradyphrenia in HD, and was limited to a sample of just 12 patients with choreiform movements and considerable functional impairment (a mean Unified

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Huntington's Disease Rating Scale (UHDRS) Total Capacity Score (TFC) of 2.8). The lack of rigorous investigation of bradyphrenia in HD is surprising, as HD was one of the first disorders within which the concept of subcortical dementia – characterized in part by a slowness of mental processing – was first recognized [7,8]. In addition, we have recently shown that cognitive processing deficits appear to arise during the prodromal and manifest stages of HD, as quantified using the Computerized Test of Information Processing (CTiP) [9]. Notably, while the CTiP has been used to measure cognitive processing in studies of traumatic brain injury [10] and, predominantly, multiple sclerosis [11–15], to our knowledge we are the first to utilize this measure in the field of HD research.

Huntington's Disease is a neurodegenerative disorder caused by a hereditary, autosomal dominant mutation in the *Huntingtin (HTT)* gene. This mutation, which presents as an abnormal number (>35) of trinucleuotide (CAG) repeats in exon 1 of the *HTT* gene, produces insidious mid-life deterioration, followed by a premature death approximately 20 years after onset. Often, decline begins with the onset of cognitive and psychiatric symptoms, followed by motoric deficits as required for a clinical diagnosis of manifest HD. For the purposes of clinical research, the Huntington's Disease Integrated Staging System (HD-ISS) was recently developed, to categorize individuals with the *HTT* mutation into disease progression cohorts based on cognitive, motoric, and functional symptom thresholds [16]. The aim of the current study was thus to investigate the possible existence and significance of bradyphrenia across the spectrum of HD disease progression, operationalized using the CTiP. The CTiP is an easy to administer, objective and time-efficient computerized test that assesses reaction times across two sub-tests of increasing cognitive difficulty. The utilization of two sub-tests of increasing difficulty makes the CTiP more conducive to the assessment of bradyphrenia, compared to other neuropsychological tests such as the semantic verbal fluency test and Stroop test. In addition, the CTiP also includes a simple reaction time task, making it more advantageous than the Symbol Digit Modalities Test and Trail Making Test for this type of assessment as it allows for the examination of central cognitive processing speed by using motor-corrected scores to account for motor dysfunction [17,18].

2. Methods

2.1. Participants

Carriers of the *HTT* genetic mutation with a familial history of the disorder (herein referred to as HD mutation carriers), as well as healthy controls (HC) who were not at risk of inheriting the *HTT* mutation, were recruited from the University of California, San Diego (UCSD) Huntington's Disease Society of America (HDSA) Center of Excellence (CoE). All HC had a Montreal Cognitive Assessment (MoCA) score of 26 or higher [19], and were not related by blood to a HD mutation carrier (i.e were never at risk of inheriting the HD genetic mutation). All individuals who were eligible, had consented, and completed a clinical research visit inclusive of the CTiP (as part of a larger clinical battery) at UCSD HDSA CoE, were included. Demographic and disease data were also collected at the time of participation, including gender, age, CAG repeat length, and years of education.

This study was approved by the UCSD Institutional Review Board, in accordance with the requirements of the Code of Federal Regulations on the Protection of Human Subjects. All participants gave written informed consent prior to participation.

2.2. Clinical assessment

Clinical research visits included assessments of cognitive, functional, and motor ability. The cognitive battery included the MoCA (score range 0–30) [19], Symbol Digit Modalities Test (SDMT; score range 0–110) [20] and Stroop Word Reading test (SWR; quantified as the number of color names read in 45 s). Functional ability and motor dysfunction were evaluated using the UHDRS [21] TFC (score range 0–13), and Total Motor Score (TMS, score range 1–124) assessments, respectively. A composite UHDRS (cUHDRS) score, based on the SWR, SDMT, TFC and TMS, was also calculated for each visit as an additional measure of disease burden [22]. The Prognostic Index Normed (PIN) score, developed as a means of predicting HD disease progression in terms of proximity to future manifest HD diagnosis[23], was also calculated using a previously published formula, which incorporates a participant's age, CAG repeat length, SDMT score, and TMS score [23]. In addition, due to previously reported associations between depression and bradyphrenia [1,24],participant depression ratings were obtained using the depression subscore of the Hospital Anxiety and Depression Scale (HADS).

2.3. HD-ISS categorization

HD mutation carriers were categorized into HD-ISS stages. The HD-ISS is comprised of four stages: Stage 0 describes participants carrying the *HTT* mutation, but without symptom presentation or detectable pathological change; Stage 1 describes those exhibiting underlying basal ganglia pathology as measured by quantitative magnetic resonance imaging; Stage 2 describes those displaying a clinical phenotype as measured by changes on the SDMT and/or TMS; and Stage 3 describes those demonstrating functional decline as measured by changes on the UHDRS TFC score and/or Independence score [16]. However, for many research sites the collection of quantitative neuroimaging data is not feasible and subsequently, the authors of the HD-ISS have provided PIN score thresholds that are estimated to maximize separation of the HD-ISS groupings [16,25,26]. For this study, HD-ISS categorization was estimated according to a participant's PIN score. Specifically, participants with a PIN score <=-0.34 were categorized as Stage 0, those with a PIN score of > -0.34 – 0.60 as Stage 1, those with a PIN score of > 0.60 – 2.31 as Stage 2, and those with a PIN score greater than 2.31 as Stage 3 [16,25,26].

2.4. Computerized Test of Information Processing (CTiP)

The CTiP was performed as previously described, using CTIP 5.0 (Build 2, via Multi-Health Systems, ON, CA) [9,17,18]. Briefly, the participant completed three computerized response time (RT) subtests, each consisting of 30 trials preceded by 10 practice trials. Administration of the CTiP takes about 15 min, or 5 min per subtest. In the first subtest, which measured Simple Reaction Time (SRT), the participant was asked to press a spacebar using their dominant hand as soon as a single stimulus (an 'X') appeared in the center of the screen. This provided a measure of motor response, in the absence of a cognitively demanding task. In the second subtest, which measured Choice Reaction Time (CRT), the participant was asked to press a key with their left index finger ('Z') when the word 'DUCK' appeared on the screen, and a key with their right index finger ('?') when the word 'KITE' appeared on the screen; each stimulus was presented an equal number of times. This second subtest was a measure of reaction time associated with a low cognitively demanding, decisional component. The third test, which measured Semantic Search Reaction Time (SSRT), required conceptual/semantic processing, by asking a participant to decide whether a word that appears on the screen belonged to the category displayed above it ('Z' with their left index finger for 'yes', '?' with their right index finger for 'no'). For example, if the category was 'Tool' and the word was 'Hammer', the correct key would be 'Z'; if the word was 'Sofa' the correct key would be '?'. The mean reaction time for 30 replicates of each subtest was taken as the uncorrected, dependent variable for each subject. The aim of this study was to operationalize and quantify bradyphrenia, using a measure of central conduction time that is exclusive of a motor component. For this purpose, SRT values were subtracted from CRT and SSRT values to obtain motor-corrected CRT and SSRT values.

The difference between these motor-corrected values [(SSRT-SRT)-(CRT-SRT)] was calculated in the current study to assess how cognitive processing reaction times varied with tasks of increasing complexity and HD progression. All CTiP assessments were conducted using Windows 7, on a Sony Vaio laptop with a 11.3″ x 7.1″ LCD screen.

2.5. Statistical analysis

Analyses were conducted with GraphPad Prism version 8.4.2 (GraphPad Software, La Jolla, CA, USA). Assumptions of normality were checked using Shapiro-Wilks test and between-group comparisons of continuous data were subsequently conducted via One-Way ANOVA or Kruskall-Wallis test, as appropriate. Within-group comparisons of CRT-SRT versus SSRT-SRT values were conducted via Mann-Whitney *U* test. A preliminary analysis of cohort and test condition interaction effect was conducted by two-way ANOVA. As participants were placed in HD-ISS stages based on their PIN score, and the PIN score equation accounts for age and CAG repeat length, additional adjustments for these covariates were not made [16,23,25,26].

3. Results

3.1. Participant characteristics

211 participant visits were included in this study, including HD-ISS Stage 0 [n = 28], Stage 1 [n = 30], Stage 2 [n = 48], and Stage 3 [n = 48], as well as healthy controls (HC) [n = 57]. Cohort demographic and clinical characteristics are presented in Table 1. HC data is provided as a qualitative indication of the general population range of responses, but was not included in analyses. HD-ISS categories differed significantly in median age, with Stage 0 participants younger than all other cohorts (Stage 0 vs Stage 2, and Stage 3 p values < 0.0001; Stage 0 vs Stage 1 $p = 0.001$). Stage 0 ($p < 0.0001$) and Stage 1 ($p = 0.003$) had significantly fewer CAG repeats compared to Stage 3. All cohorts differed significantly in TFC scores except for Stage 1 compared to Stage 0 and Stage 2 (Stage 0 vs Stage 2 p = 0.001; all other p values < 0.0001). All cohorts differed significantly in TMS scores except for Stage 0 compared to Stage 1 (Stage 1 vs Stage 2 $p = 0.003$, all other p values < 0.0001). All cohorts differed significantly in SDMT scores (Stage 0 vs Stage 1 $p = 0.01$; all other ps < 0.0001). MoCA scores differed significantly when comparing Stage 0 to Stage 2 (p = 0.006), and to Stage 3 (p < 0.0001); as well as Stage 1 ($p < 0.0001$), and Stage 2 ($p = 0.03$) compared to Stage 3. Composite UHDRS scores differed significantly between all cohorts (all p values < 0.0001), except for Stage 0 compared to Stage 1. Years of education, and Hospital Anxiety and Depression Scale (HADS) depression sub-scores, did not differ across HD-ISS categories.

3.2. Comparison of CTiP reaction times within cohorts

Median unadjusted (SRT, CRT, SSRT) and motor-adjusted (CRT-SRT, SSRT-SRT) values by HD-ISS category, as well as in healthy controls, are presented in Table 2.

All within-cohort reaction times differed significantly when comparing CRT-SRT vs SSRT-SRT (all p values < 0.0001; all effect sizes (r) = 0.71–0.77) (Fig. 1A-E; see Table 2 for reaction time values). Furthermore, within-subject differences between CRT-SRT and SSRT-SRT values increased with HD disease stage (Kruskal-Wallis $\chi^2 = 26.88$, p < 0.0001) (Fig. 1F). Post-hoc analyses revealed significant differences in these values [(SSRT-SRT)-(CRT-SRT)] when comparing Stage 3 to Stage 1 (p = 0.0007), and to Stage 0 (p < 0.0001) (Fig. 1F). This observed increase in within-subject [(SSRT-SRT)-(CRT-SRT)] values from HD-ISS Stage 1 to Stage 3 prompted us to conduct an unplanned, post-hoc Receiver Operating Characteristic (ROC) Curve analysis, to determine whether [(SSRT-SRT)-(CRT-SRT)] values may assist in identifying participants near or at manifest HD onset (approximating to Stage 2 and Stage 3 combined). [(SSRT-SRT)-(CRT-SRT)] values significantly distinguished Stage 2 + 3 from Stage 0 + 1 with an Area under the ROC Curve (AUC) of 0.72 (p < 0.0001). The [(SSRT-SRT)-(CRT-SRT)] value that most greatly distinguished Stage 2 + 3 from Stage 0 + 1, using Youden's Index[27], was > 0.495 sec (sensitivity = 54.84 %, specificity = 86.21 %), followed by > 0.565 sec (sensitivity = 49.46 %, specificity = 91.38 %).

We also conducted a preliminary two-way mixed effects ANOVA of CTiP test measure by cohort, to investigate the potential contributions of test complexity and cohort towards the above within-cohort findings.

Table 1
Cohort characteristics [median, interquartile range].

	Healthy Controls	**Stage 0**	**Stage 1**	**Stage 2**	**Stage 3**	
n	57	28	30	48	48	
						Kruskal-Wallis or Chi Square χ^2, p
Age [years]	54.0, 40.5–64.0	33.0, 28.3–38.0	50.0, 38.5–57.3	51.5, 41.3–60.8	53.0, 42.0–60.8	35.3, <0.0001
Gender n[M/F]	28/29	11/17	15/15	22/26	20/28	1.27, 0.87
Education [years]	16.0, 13.0–18.0	16.0, 13.0–16.8	16.0, 14.0–16.5	16.0, 13.0–16.0	14.0, 12.0–16.0	3.5, 0.32
CAG Repeat Length	N/A	41.0, 40.0–43.0	41.0, 40.0–43.3	42.0, 41.0–44.0	43.5, 42.0–47.0	23.0, <0.0001
TMS	0.0, 0.0–1.5	0.0, 0.0–2.8	3.5, 0.0–6.3	10.5, 6.0–19.8	34.5, 27.3–42.0	113.2, <0.0001
TFC	13.0, 13.0–13.0	13.0, 13.0–13.0	13.0, 13.0–13.0	12.0, 10.25–13.0	9.0, 7.0–10.0	79.21, <0.0001
MoCA	28.0, 27.0–29.0	28.0, 27.0–29.0	27.0, 25.0–29.0	25.0, 24.0–27.0	23.0, 17.3–25.0	40.3, <0.0001
HADS-D	2.0, 0.0–4.0	2.0, 0.0–7.0	4.0, 1.0–7.0	2.0, 1.0–6.0	4.0, 1.0–9.0	5.2, 0.16
						One-Way ANOVA F, *p*
CAP	N/A	254.1, 213.1–298.2	371.0, 336.4–408.0	442.2, 418.4–467.5	522.3, 472.8–560.4	104.6, <0.0001
SDMT	51.0, 45.5–57.0	57.0, 51.3–61.0	47.5, 43.0–53.5	36.5, 30.3–46.0	24.5, 20.0–28.0	87.3, <0.0001
cUHDRS	17.2, 16.8–17.9	17.5, 16.8–18.4	16.6, 15.6–17.7	14.5, 12.3–15.6	10.1, 8.5–11.3	131.5, <0.0001

cUHDRS, composite Unified Huntington's Disease Rating Scale; F, female; M, male; MoCA, Montreal Cognitive Assessment; HADS-D, Hospital Anxiety and Depression Scale – Depression subscale; TMS, Total Motor Score; SDMT, Symbol Digit Modalities Test. Healthy Controls representative the general population range of responses and are presented for qualitative purposes only; they were not included in analyses.

Table 2
Cohort reaction times [median, interquartile range].

Cohort		Measure			Motor-corrected		
		SRT	CRT	SSRT	CRT-SRT	SSRT-SRT	p value
Healthy Controls		0.33, 0.31–0.38	0.60, 0.53–0.68	0.93, 0.79–1.04	0.24, 0.30–0.32	0.57, 0.47–0.70	<0.0001
HD-ISS	**Stage 0**	0.35, 0.32–0.40	0.58, 0.53–0.72	0.93, 0.81–0.99	0.24, 0.16–0.35	0.53, 0.44–0.66	<0.0001
	Stage 1	0.37, 0.35–0.41	0.68, 0.60–0.76	1.06, 0.87–1.22	0.30, 0.22–0.36	0.65, 0.51–0.83	<0.0001
	Stage 2	0.40, 0.34–0.47	0.67, 0.61–0.88	1.18, 0.93–1.48	0.30, 0.24–0.39	0.73, 0.57–1.07	<0.0001
	Stage 3	0.51, 0.44–0.73	0.97, 0.82–1.15	1.66, 0.34–2.11	0.45, 0.31–0.61	1.09, 0.94–1.42	<0.0001

SRT, Simple Reaction Time; CRT, Choice Reaction Time; SSRT, Semantic Search Reaction. Within-group comparisons of CRT-SRT versus SSRT-SRT values were conducted via Mann-Whitney *U* test.

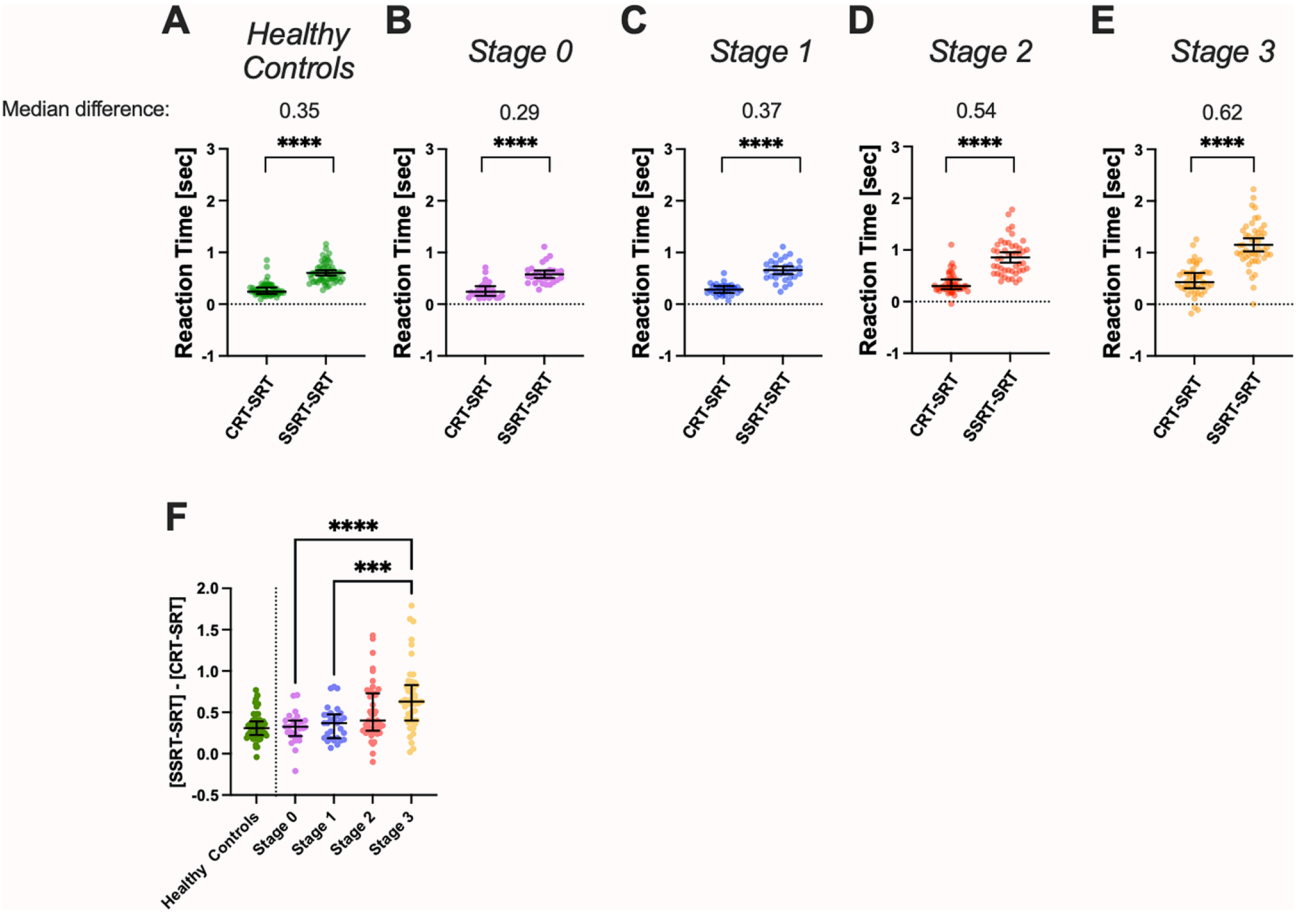

Fig. 1. A comparison of motor (Simple Reaction Time (SRT)) - adjusted values for Choice Reaction Time (CRT-SRT) and Semantic Search Reaction Time (SSRT-SRT), in Huntington's Disease Integrated Staging System (HD-ISS) categorized participants, and healthy controls. Panels A-E show the motor-adjusted reaction times for healthy controls (A), as well as HD-ISS Stage 0 (B), Stage 1 (C), Stage 2 (D), and Stage 3 (E). All within-group analyses of test complexity, conducted via Mann-Whitney *U* test, were significant (****p < 0.0001). Panel F, conducted via Kruskal-Wallis test, shows a comparison of motor-corrected differences in CRT and SSRT reaction times, across HD-ISS categorized participants (Stage 0 – Stage 3); healthy controls are presented for qualititative comparison but were not included in the analysis. Errors bars are median +/- interquartile range.

This analysis demonstrated significant Type III fixed effects for test complexity ($F_{1,203} = 481.5$, $p < 0.0001$), cohort ($F_{4,205} = 27.4$, $p < 0.0001$), and interaction effect ($F_{4,203} = 13.75$, $p < 0.0001$) on motor-corrected reaction times.

4. Discussion

We have previously shown that deficits in central cognitive processing, as measured by the CTiP CRT-SRT and SSRT-SRT measures, become apparent during the prodromal and manifest HD stages [9]. The present study builds on these findings, by showing that the within-group reaction time differences *between* choice (CRT-SRT) and semantic search (SSRT-SRT) responses, corrected for motor performance, increase with HD disease stage. Furthermore, these within-subject, between-test differences may distinguish the prodromal and manifest participants (Stage 2 + 3) from clinically sub-threshold participants (Stage 0 + 1). Our

findings suggest the presence of bradyphrenia in later stages of HD.

The presence of bradyphrenia has previously been investigated in neurodegenerative disorders, including PD and other lewy body dementias [1,4], as well as in schizophrenia [5]. In PD, variations in cohort characterization, and operationalization of bradyphrenia, have contributed to conflicting results [28]. In schizophrenia, patients displayed increased pause frequency and duration during free-speech, compared to rote-speech [5], however no difference in thinking time on the Tower of London test, at any level of item complexity, compared to controls [6]. In the same latter study, PD patients differed significantly from controls in thinking time for Tower of London items involving 6, 7, and 8 move solutions, and HD patients differed from controls for items involving 6 and 8 moves [6]. Interestingly, while basal ganglia neurodegeneration is common to both PD and HD, the striatum is also involved in the coordination of motor, cognitive and behavioral functions required for the production of speech. Therefore, these findings of bradyphrenia in schizophrenia [5], and in PD and HD [6], may represent different phenotypes with similar pathophysiological underpinnings.

It is important to note that control, HD, PD and schizophrenia cohorts in the Tower of London study by Hanes and colleagues differed on motor performance (as measured by Purdue Pegboard), Beck Depression Rating, and Premorbid IQ (as measured by the National Adult Reading Test), and these factors were not accounted for. In addition, Hanes and colleague did not consider within-disease sub-cohorts [6]. This is significant, as others have previously contended that population heterogeneity across studies can contribute noise to analyses and determinations of bradyphrenia [28].

In our study, in line with Hanes' findings on bradyphrenia in HD, we have similarly shown a significant Group x Item Complexity interaction effect using the CTiP. Morever, the use of motor-corrected scores in our study conveys that our findings are indicative of bradyphrenia, and not differences in motor performance (e.g bradykinesia). We contend that the CTiP is an advantageous means of operationalizing bradyphrenia. The CTiP is an automated and timed computerized test, which removes the potential for inter-rater variability in administration. Second, measures of CRT and SSRT are completed sequentially, allowing for a direct comparison of test complexity-related reaction times within the same external environment and visit. Third, as aforementioned, the incorporation of a SRT test allows for the correction of motor dysfunction inherent to HD disease progression. Our data also showed that disease stage cohorts did not differ in their reported experience of depression, suggesting that depressive symptoms do not explain the slowed cognitive processing observed in our HD sample.

As one would expect, the HD-ISS disease progression cohorts in our study differed in cognitive function, as measured by the SDMT and MoCA. Notably, the SDMT is also a measure of cognitive processing speed [20], incorporated into our PIN score-estimated HD-ISS categorization [23]; for these reasons, it is expected that SDMT values would decrease with increasing disease burden. Regarding the MoCA, our study was predominantly focused on within-subject and within-group analyses – comparisons of reaction times by increased test complexity – and therefore we expect that any cognitive decline as measured by the MoCA would affect both CRT and SSRT conduct similarly. Moreover, the capability to *correctly respond to questions,* as measured by the MoCA, is different from the *time taken to* process a response. While the SDMT does assess both the extent to which an individual can complete the test, as well as the speed (or completion rate) at which this is done, the CTiP is once again advantageous as it includes a measure of SRT, which may then be subtracted from the more cognitively taxing CTiP tasks in order to obtain motor-corrected, central cognitive conduction times [9]. Conversely, the SDMT, and visuospatial/executive measures of the MoCA, may be impacted by elements of both bradykinesia and akinesia.

Regarding potential study limitations, the presence of medication use may be a confound that could not fully be accounted for in our study; however, we contend that by using motor-corrected scores, we indirectly account for potential differences contributed to by the use of VMAT2 inhibitors, neuroleptics or other medications [29,30]. We also acknowledge that undiagnosed, undetected or unreported learning difficulties, such as a dyslexia, may be present in the study population and could affect performance on the CTiP. Finally, we note that impairments in executive functioning or semantic verbal skills may contribute to the quantification of bradyphrenia in our study. Our previous analysis of cognitive processing in HD, as measured by the CTiP, displayed greater reaction times for the CRT compared to the SRT, suggesting that this increase is not purely due to differences in semantic verbal skills [9]; however, further research into bradyphrenia would benefit from the inclusion of additional levels of cognitive difficulty.

Overall, our findings imply the presence of bradyphrenia in HD, which becomes more apparent at later disease stages. Furthermore, we have found that median within-participant differences between motor-corrected, CRT and SSRT values [(SSRT-SRT) – (CRT-SRT)] may distinguish prodromal and manifest HD participants. We contend that the CTiP is a unique and advantageous means of quantifying bradyphrenia in neurodegenerative disorders that with additional research may prove useful in furthering our understanding of HD progression.

CRediT authorship contribution statement

Georgia M. Parkin: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Braden Culbert:** Data curation, Writing – review & editing. **Emma Churchill:** Data curation, Writing – review & editing. **Paul E. Gilbert:** Conceptualization, Methodology, Writing – review & editing. **Jody Corey-Bloom:** Conceptualization, Methodology, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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