Published in final edited form as:
Mov Disord. 2014 September 15; 29(11): 1342–1350. doi:10.1002/mds.25997.

Onset of Huntington disease: Can it be purely cognitive?

Jane S. Paulsen[1,2,3,*] and **Jeffrey D. Long**[1,4]

[1]Department of Psychiatry, Carver College of Medicine, The University of Iowa, Iowa City, IA, USA

[2]Department of Neurology, Carver College of Medicine, The University of Iowa, Iowa City, IA, USA

[3]Department of Psychology, The University of Iowa, Iowa City, IA, USA

[4]Department of Biostatistics, College of Public Health, The University of Iowa, Iowa City, IA, USA

Abstract

Knowledge of the cognitive manifestation of Huntington disease has burgeoned over the past two decades. Many studies from independent datasets have shown cognitive impairment is evident prior to motor diagnosis and annual cognitive decline is a robust marker of disease progression. Additionally, cognition is a critical concern to patients and families and is associated with meaningful outcomes including functional capacity, driving, loss of accustomed work and quality of life. In the past few years, Huntington disease animal models of cognition have increased, preparing for preclinical experimental therapeutics with cognitive endpoints. A longitudinal analysis of cognitive variables was conducted with 559 gene-positive cases and 233 controls showing no signs of motor abnormalities over approximately a three year period. Results show there were statistically significant differences in rate of annual change for some cognitive variables, such that the cases group had worsening performance over time. These findings show cognitive deterioration can be seen in persons with the Huntington disease gene expansion with no overt motor signs or symptoms, suggesting that cognitive onset of Huntington disease may precede motor.

Keywords

Huntington disease; cognition; non-motor; onset; diagnosis

[*]**Correspondence to:** Jane S. Paulsen, Carver College of Medicine, Carver Chair in Neuroscience and Professor of Neurology, Psychiatry and Psychology, 1–305 Medical Education Building, Iowa City, IA 52242-1000, USA. 319-353-4551, predict-publications@uiowa.edu; jane-paulsen@uiowa.edu.

Author Roles

J.S.P. and J.D.L. contributed to conception, organization and execution of the research project; design and review/critique for the statistical analysis; and writing of the first draft and review and critique of the manuscript. J.D.L. provided execution of the statistical analysis.

Financial Disclosures

Dr. Paulsen has served on an advisory board for Lundbeck, LLC, and has a consulting agreement with ProPhase, LLC. Dr. Long has a consulting agreement with NeuroPhage, LLC.

The motor signs and symptoms of Huntington disease (HD) have maintained a prominent role in clinical care and research since the initial identification of the disease.[1] The importance of cognition in HD has slowly increased over the years. The purpose of this viewpoint is to briefly summarize the significance of cognition in the following areas: (1) Detection of onset; (2) Tracking disease progression; (3) Patient-centered outcomes; and (4) Disease mechanism and intervention. Finally, data are reviewed and analyzed to examine whether the cognitive decline of HD can occur in the absence of motor manifestation.

Cognitive Assessment To Detect HD

Knowledge of the cognitive manifestation of HD has burgeoned over the past two decades. A recent review reported over 1000 publications of cognition in HD.[2] The largest study to examine early detection of cognitive impairments in premanifest disease examined 906 participants on a comprehensive battery of 19 cognitive tests and computed differences between premanifest HD and normal controls on 51 variables.[3] A truncated summary of these findings is shown in Table 1. Premanifest HD research participants are divided into subgroups to demarcate stages of prodromal disease severity. Efforts to stage premanifest disease have typically been derived from a combination of genetic, demographic and clinical criteria. In this article, subgroups of prodromal HD were derived from formulae using the CAG repeat length and current age to estimate number of years to motor diagnosis.[4] Groups were estimated as follows: “near” motor diagnosis or within 7 years; “mid” to motor diagnosis or from 7-to-12 years; and “far” from motor diagnosis or more than 12 years to motor diagnosis. Additional analyses showed cognitive measures tap unique variance in proximity to diagnosis that is not captured by the motor exam. The cognitive battery accounted for 34% of the variance in age of onset; in comparison, the total motor score accounted for 11.7%.

Tracking Disease Progression with Cognition

We recently reviewed all articles emphasizing cognitive decline in persons considered premanifest for HD and compared data from nearly 1300 participants to those in the literature.[5] Results indicated insidious and significant cognitive decline over time was evident for 21 cognitive measures. A brief summary is presented in Table 2 and shows cognitive decline is evident in persons at all stages of the HD prodrome. In this article, premanifest HD research participants were divided into subgroups to demarcate stages of prodromal disease severity based on probability of receiving a motor diagnosis within the next five years. A formula validated from prospectively diagnosed patients was used[6] to establish the following groups: High probability of motor diagnosis within five years; Medium probability of diagnosis within five years; or Low probability of motor diagnosis within five years. At-risk research participants without the gene expansion were used as controls (See Figure 1). Most recently, cognitive decline was compared between two premanifest gene-expanded HD groups: those who showed conversion to manifest HD based upon the motor diagnosis and those similarly followed who did not receive an HD motor diagnosis. See Figure 2 for illustration of the natural history of cognitive decline in HD in these subgroups. Many additional researchers and participant samples have replicated these findings.[2, 7–9]

Importance of Cognition for Patient-Centered Outcomes

It is the position of the U.S. Food and Drug Administration (FDA) that in addition to reliable assessment of change, cognitive measures should index a clinically meaningful functional outcome.[10, 11] Thus, evidence of cognitive decline in HD needs to be closely tied to reports by the patient (and therefore also the clinician) that such impairments impact life and/or interfere with day-to-day functioning. Efforts to obtain patient-centered outcomes for HD have been undertaken by several researchers using qualitative methods such as focus groups,[12, 13] semi-structured interviewing,[14–19] as well as quantitative data analyses using standardized outcomes.[20] Findings are consistent across methods and studies, showing cognitive impairments are a prominent concern shared by patients and families and are associated with meaningful outcomes including motor diagnosis,[21] functional capacity,[22–24] driving,[23] loss of accustomed work,[24] sleep and circadian rhythm alterations,[25] and quality of life.[26–29] More specifically, Beglinger and her colleagues[23] conducted one of the most detailed analyses involving predictors of patient-centered outcomes and reported performance on the Stroop Interference Task was associated with functional loss for the ability to manage finances, drive safely, supervise children, volunteer, and grocery shop. The Symbol Digit Modalities Test was associated with inability to grocery shop and use public transportation. Cognition has been researched both as an independent predictive factor as well as a predictive factor when combined with other clinical features, such as behavioral and motor symptoms.[30] Findings have suggested cognitive impairments account for a unique and significant portion of the variance in functional capacity beyond that of demographic, motor and psychiatric variables.[31]

Disease Mechanism and Intervention

The best clinical signs and symptoms of disease are those for which conceptual frameworks and biological theories can be utilized to enhance understanding and synergize translation of new findings from bench to bedside and back. Increased understanding of how striatal dysfunction contributes to motor abnormality has led to improvement in pharmacological and surgical therapies for many movement disorders; the same cannot be said for cognition. The role of the striatum in a range of cognitive processes has been well characterized in several human and animal studies by its anatomical positioning as a pivotal component of cortico-subcortical circuits (see Figure 3 for illustration).[32] Vonsattel and DiFiglia[33] have articulated the course of HD pathology from the dorsal caudate head through the ventrolateral striatum. For decades, knowledge of complex cognitive functions associated with the striatum has developed. With recent advances suggesting cognitive impairments precede motor signs in HD by a decade, animal models are now being probed for the specific cognitive deficits represented in human disease states. Brooks and Dunnett[34] examined preclinical cognitive measures in animal models of HD to determine the viability of selecting cognition as a potential therapeutic target. For example, early cognitive impairments were detected in the HD 51 CAG transgenic rat model, as measured by the Spatial Operant Reversal Test, prior to motor deficits, gross anatomical changes or cell loss.[35] In another study, memory deficits in an HD knock-in mouse model were associated with CREB-binding protein and diminished levels of histone H3 acetylation,[36] suggesting therapeutic interventions for cognitive decline. Harrison and his colleagues[37] showed

exercise intervention in R6/1 HD mice slowed cognitive progression as measured by the water T-maze learning paradigm. These and similar studies may expand treatment options for persons suffering with HD, even in early stages of disease prior to motor onset.

Can Cognitive Onset Occur in the Absence of Motor Manifestation?

It has become increasingly apparent that HD has a broad range of cognitive abnormalities that manifest prior to the onset of overt motor dysfunction, providing opportunities for earlier clinical care. It has been shown that “mild cognitive impairment” is present in up to half of premanifest persons close to motor diagnosis[38] and formal cognitive assessment in persons with known gene mutation can facilitate compensatory strategies for subtle cognitive impairments, potentially maximizing functional capacity and quality of life. The trajectory of cognitive impairment with the traditional motor disease course, however, remains unclear. Biglan and his colleagues[39] compared two methods of HD diagnosis and found a large proportion of cases were given an earlier diagnosis when movement disorder specialists were allowed to consider all clinical information, including cognitive performance. To our knowledge, no study has considered whether cognitive decline believed secondary to the expanded HD allele can be used to detect active disease in persons without any motor abnormality. The purpose of the brief study below was to test this hypothesis.

Study Method

Participants

Participants were a subsample of N = 792 individuals from the larger PREDICT-HD study, with 559 gene-positive cases defined by CAG > 35, and 233 controls (CAG ≤ 35). Data were collected from 2001 to 2012 and all participants had prior and independent genetic testing for HD. Dropout was less than 5% per year in the larger study. Exclusion criteria included the presence of other central nervous system disease, injury, or developmental disorder, or evidence of an unstable medical or psychiatric illness. All participants provided informed consent (approved by respective institutional review boards) and were treated consistent with ethical standards.[40] For this analysis we selected only those time points with a rating of “normal” (no abnormalities) on the UHDRS Diagnostic Confidence Level (DCL). Table 3 shows descriptive statistics by group. There was sample size variation among the outcome variables (see Figure 4) due to design changes that occurred across three separate National Institutes of Health funding periods. The percentages in Table 3 were similar among the different sample sizes (e.g., the percentage of females in a group was similar for all variables).

Statistical analysis

The analysis focused on case and control group differences in rate of change of 10 cognitive variables and the UHDRS total motor score (TMS) included for comparison. Linear mixed effects regression (LMER) was used to fit linear change curves for the repeated measures under which the participants were rated with DCL = 0 (no motor abnormalities). The time metric was years in the study, also known as duration. Each outcome variable was analyzed separately and standardized to facilitate comparison. The following covariates were included

to control for pre-existing group differences (see Table 3): gender, examiner knowledge of gene status (blinding), age at study entry, year of education at study entry, and number of repeated measures (waves of observation). Preliminary analysis not presented indicated linear curves were adequate for modeling change over time. Random effects for intercept, slope, and site (to account for site-to-site variation) were included in all models. The object of inference was the difference of the case and control slopes. Details of the LMER modeling are provided in the Appendix.

Study Results

Figure 4 shows the results of the LMER analysis of slope differences. Sample size is in parentheses next to each variable label. The point estimate of a standardized absolute value slope difference is represented by a filled circle, and the 95% confidence interval (CI) is indicated by a solid horizontal line. Zero difference is denoted by the vertical dashed line. If a CI does not contain zero, then the null hypothesis of equal slopes (zero slope difference) is rejected. As the figure shows, the TMS CI (top) contained zero, indicating the null hypothesis was not rejected. Cognitive variables for which the null hypothesis was rejected are listed in the order of the point estimate effect: Trail Making Test, Part A, Symbol Digit Modalities Test, University of Pennsylvania Smell Identification Test (UPSIT), Stroop Color and Word Test – interference condition, and Stroop Color and Word Test – color condition. To adjust for multiple testing, we also considered 99% CIs and the null hypothesis was rejected for Trail Making Test, Part A and Symbol Digit Modalities Test. Figure 5 shows the fitted linear curves for the two top variables based on the estimated LMER models (controlling for the covariates) and retaining the original scale of the variables. Lower scores on the Trail Making Test, Part A and higher scores on the Symbol Digit Modalities Test indicate better performance. As the figure illustrates, both the case and control groups showed practice effects, with performance improving over time. However, the case group showed a statistically significant slowing of the practice effects.

Correlations between the cognitive performances and traditional functional variables were evaluated to examine the clinical significance of these early cognitive symptoms. The Total Functional Capacity and the Functional Assessment Scale from the Unified Huntington's Disease Rating Scale were highly associated with numerous cognitive performances (i.e., p-values < 0.001) with correlations ranging from .17 for the Stroop Interference subtest to −.26 for the Trail Making Test Part B.

Discussion

We examined whether case and control differences might develop for cognitive variables when both groups show no detectible signs of motor abnormalities. To verify the absence of motor abnormalities, we selected observations for which DCL = 0. Beyond the fact that we found no case and control difference in TMS rate of change (see Figure 4), additional results not presented show the estimated rate of change for both groups was very close to zero and not statistically different from zero. Furthermore, the tapping variables (paced and speeded) that had a motor component also showed no significant group slope difference. Therefore,

we are confident that the individuals considered in our analysis did not develop or display motor abnormalities in the period of study.

Our key finding is that there was a statistically significant difference in rate of change for the Trail Making and Symbol Digit Modalities tests, such that the case group had poorer performance over time relative to the control group. The study period represented early HD progression for all participants and as such, practice effects among the cases and controls were evident (see Figure 5). The important result was a diminishing of practice effects for the cases group. Such diminution of performance is evidence of non-motor HD onset. DCL = 0 can occur decades prior to motor diagnosis[41, 42] indicating certain cognitive variables might index very early disease effects. The results are evidence that HD onset, in the form of cognitive impairment, might develop at a time much earlier than the onset of motor abnormalities.

Findings validate and extend previous studies suggesting cognitive manifestation of HD occurs before its motor manifestation. For instance, O'Rourke and his colleagues[43] examined the contributions of motor, psychiatric and cognitive changes to Trail Making Test scores and demonstrated that motor signs only mildly affected cognitive performances whereas perceptual processing, visual scanning, attention, response inhibition, set-shifting, processing speed and working memory were more highly associated with cognitive outcomes.

It is important to emphasize the current study and extant literature reflect primarily group data and suggest cognitive often precedes motor manifestation, although individual cases can present with heterogeneous manifestations of disease and each individual should be carefully examined for cognitive, motor, functional and psychiatric symptoms and signs. These research findings have important implications for future selection of research participants, the determination of outcome measures for clinical trials and reconsideration of the current criteria for clinical diagnosis of HD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial Disclosures/Conflict of Interest/Funding sources for study

This research is supported by the National Institutes for Health, National Institute of Neurological Disorders and Stroke (5R01NS040068) awarded to Dr. Paulsen, CHDI Foundation, Inc (A3917) awarded to Dr. Paulsen, Cognitive and Functional Brain Changes in Preclinical Huntington's Disease (HD) (5R01NS054893) awarded to Dr. Paulsen.

We thank the PREDICT-HD sites, the study participants, the National Research Roster for Huntington Disease Patients and Families, the Huntington's Disease Society of America and the Huntington Study Group. This publication was supported by the National Center for Advancing Translational Sciences, and the National Institutes of Health (NIH), through Grant 2 UL1 TR000442-06. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

References

1. Huntington G. On Chorea. The Medical and Surgical Reporter: A Weekly Journal. 1872; 26:317–321.
2. Dumas EM, van den Bogaard SJ, Middelkoop HA, Roos RA. A review of cognition in Huntington's disease. Front Biosci (Schol Ed). 2013; 5:1–18. [PubMed: 23277034]
3. Stout JC, Paulsen JS, Queller S, et al. Neurocognitive signs in prodromal Huntington disease. Neuropsychology. 2011; 25:1–14. [PubMed: 20919768]
4. Langbehn DR, Brinkman RR, Falush D, Paulsen JS, Hayden MR. International Huntington′s Disease Collaborative Group. A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. Clin Genet. 2004; 65:267–277. [PubMed: 15025718]
5. Paulsen JS, Smith MM, Long JD. PREDICT-HD investigators and coordinators of the Huntington Study Group. Cognitive decline in prodromal Huntington Disease: implications for clinical trials. J Neurol Neurosurg Psychiatry. 2013; 84:1233–1239. [PubMed: 23911948]
6. Zhang Y, Long JD, Mills JA, et al. Indexing disease progression at study entry with individuals at-risk for Huntington disease. Am J Med Genet B Neuropsychiatr Genet. 2011; 156B:751–763. [PubMed: 21858921]
7. Verny C, Allain P, Prudean A, et al. Cognitive changes in asymptomatic carriers of the Huntington disease mutation gene. Eur J Neurol. 2007; 14:1344–1350. [PubMed: 17941857]
8. Hahn-Barma V, Deweer B, Durr A, et al. Are cognitive changes the first symptoms of Huntington's disease? A study of gene carriers. J Neurol Neurosurg Psychiatry. 1998; 64:172–177. [PubMed: 9489526]
9. Paulsen JS. Cognitive impairment in Huntington disease: diagnosis and treatment. Curr Neurol Neurosci Rep. 2011; 11:474–483. [PubMed: 21861097]
10. Buchanan RW, Davis M, Goff D, et al. A summary of the FDA-NIMH-MATRICS workshop on clinical trial design for neurocognitive drugs for schizophrenia. Schizophr Bull. 2005; 31:5–19. [PubMed: 15888422]
11. Patrick DL, Burke LB, Powers JH, et al. Patient-reported outcomes to support medical product labeling claims: FDA perspective. Value Health. 2007; 10(Suppl 2):S125–S137. [PubMed: 17995471]
12. Vaccarino AL, Sills T, Anderson KE, et al. Assessment of cognitive symptoms in prodromal and early huntington disease. PLoS Curr. 2011; 3 RRN1250.
13. Vaccarino AL, Sills T, Anderson KE, et al. Assessment of Day-to-Day Functioning in Prodromal and Early Huntington Disease. PLoS Curr. 2011; 3 RRN1262.
14. Williams J, Downing N, Vaccarino AL, Guttman M, Paulsen JS. Self Reports of Day-to-Day Function in a Small Cohort of People with Prodromal and Early HD. PLoS Curr. 2011; 3 RRN1254.
15. Downing NR, Williams JK, Paulsen JS. Couples' attributions for work function changes in prodromal Huntington disease. Journal of Genetic Counseling. 2010; 19:343–352. [PubMed: 20309619]
16. Downing NR, Williams JK, Leserman AL, Paulsen JS. Couples' coping in prodromal Huntington disease: a mixed methods study. Jof Genet Couns. 2012; 21:662–670.
17. Penziner E, Williams JK, Erwin C, et al. Perceptions of discrimination among persons who have undergone predictive testing for Huntington's disease. Am J Med Genet B Neuropsychiatr Genet. 2008; 147:320–325. [PubMed: 17948904]
18. Williams JK, Barnette JJ, Reed D, et al. Development of the Huntington disease family concerns and strategies survey from focus group data. J Nurs Meas. 2010; 18:83–99. [PubMed: 20806651]
19. Williams JK, Erwin C, Juhl AR, et al. In their own words: reports of stigma and genetic discrimination by people at risk for Huntington disease in the International RESPOND-HD study. Am J Med Genet B Neuropsychiatr Genet. 2010; 153B:1150–1159. [PubMed: 20468062]
20. Brandt J, Strauss ME, Larus J, Jensen B, Folstein SE, Folstein MF. Clinical correlates of dementia and disability in Huntington's disease. J Clin Neuropsychol. 1984; 6:401–412. [PubMed: 6238979]

21. Harrington DL, Smith MM, Zhang Y, Carlozzi NE, Paulsen JS. PREDICT-HD Investigators of the Huntington Study Group. Cognitive domains that predict time to diagnosis in prodromal Huntington disease. J Neurol Neurosurg Psychiatry. 2012; 83:612–619. [PubMed: 22451099]
22. Marder K, Zhao H, Myers RH, et al. Rate of functional decline in Huntington′s disease. Huntington Study Group. Neurology. 2000; 54:452–458. [PubMed: 10668713]
23. Beglinger LJ, O'Rourke JJ, Wang C, et al. Earliest functional declines in Huntington disease. Psychiatry Res. 2010; 178:414–418. [PubMed: 20471695]
24. Paulsen JS, Wang C, Duff K, et al. Challenges assessing clinical endpoints in early Huntington disease. Mov Disord. 2010; 25:2595–2603. [PubMed: 20623772]
25. Aziz NA, Anguelova GV, Marinus J, Lammers GJ, Roos RA. Sleep and circadian rhythm alterations correlate with depression and cognitive impairment in Huntington's disease. Parkinsonism Relat Disord. 2010; 16:345–350. [PubMed: 20236854]
26. Helder DI, Kaptein AA, van Kempen GM, van Houwelingen JC, Roos RA. Impact of Huntington's disease on quality of life. Mov Disord. 2001; 16:325–330. [PubMed: 11295789]
27. Banaszkiewicz K, Sitek EJ, Rudzinska M, Soltan W, Slawek J, Szczudlik A. Huntington's disease from the patient, caregiver and physician's perspectives: three sides of the same coin? J Neural Transm. 2012; 119:1361–1365. [PubMed: 22398875]
28. Paulsen JS, Nance M, Kim JI, et al. A review of quality of life after predictive testing for and earlier identification of neurodegenerative diseases. Prog Neurobiol. 2013; 110:2–28. [PubMed: 24036231]
29. Ready RE, Mathews M, Leserman A, Paulsen JS. Patient and caregiver quality of life in Huntington's disease. Mov Disord. 2008; 23:721–726. [PubMed: 18175350]
30. Hamilton JM, Salmon DP, Corey-Bloom J, et al. Behavioural abnormalities contribute to functional decline in Huntington's disease. J Neurol Neurosurg Psychiatry. 2003; 74:120–122. [PubMed: 12486282]
31. Nehl C, Paulsen JS. Huntington Study Group. Cognitive and psychiatric aspects of Huntington disease contribute to functional capacity. J Nerv Ment Dis. 2004; 192:72–74. [PubMed: 14718780]
32. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci. 1986; 9:357–381. [PubMed: 3085570]
33. Vonsattel JP, DiFiglia M. Huntington disease. J Neuropathol Exp Neurol. 1998; 57:369–384. [PubMed: 9596408]
34. Brooks SP, Dunnett SB. Cognitive deficits in animal models of basal ganglia disorders. Brain Res Bull. 2013; 92:29–40. [PubMed: 22588013]
35. Fink KD, Rossignol J, Crane AT, et al. Early cognitive dysfunction in the HD 51 CAG transgenic rat model of Huntington's disease. Behav Neurosci. 2012; 126:479–487. [PubMed: 22642889]
36. Giralt A, Puigdellivol M, Carreton O, et al. Long-term memory deficits in Huntington's disease are associated with reduced CBP histone acetylase activity. Hum Mol Genet. 2012; 21:1203–1216. [PubMed: 22116937]
37. Harrison DJ, Busse M, Openshaw R, Rosser AE, Dunnett SB, Brooks SP. Exercise attenuates neuropathology and has greater benefit on cognitive than motor deficits in the R6/1 Huntington's disease mouse model. Exp Neurol. 2013; 248:457–469. [PubMed: 23911978]
38. Duff K, Paulsen J, Mills J, et al. Mild cognitive impairment in prediagnosed Huntington disease. Neurology. 2010; 75:500–507. [PubMed: 20610833]
39. Biglan KM, Zhang Y, Long JD, et al. Refining the diagnosis of Huntington disease: the PREDICT-HD study. Front Aging Neurosci. 2013; 5:12. [PubMed: 23565093]
40. Paulsen JS, Long JD, Johnson HJ, et al. Clinical and Biomarker Changes in Premanifest Huntington Disease Show Trial Feasibility: A Decade of the PREDICT-HD Study. Front Aging Neurosci. 2014; 6:78. [PubMed: 24795630]
41. Paulsen JS, Langbehn DR, Stout JC, et al. Detection of Huntington's disease decades before diagnosis: the Predict-HD study. J Neurol Neurosurg Psychiatry. 2008; 79:874–880. [PubMed: 18096682]
42. Long JD, Paulsen JS, Marder K, et al. Tracking motor impairments in the progression of Huntington's disease. Mov Disord. 2014; 29:311–319. [PubMed: 24150908]

43. O'Rourke JJ, Beglinger LJ, Smith MM, et al. The Trail Making Test in prodromal Huntington disease: contributions of disease progression to test performance. J Clin Exp Neuropsychol. 2011; 33:567–579. [PubMed: 21302170]

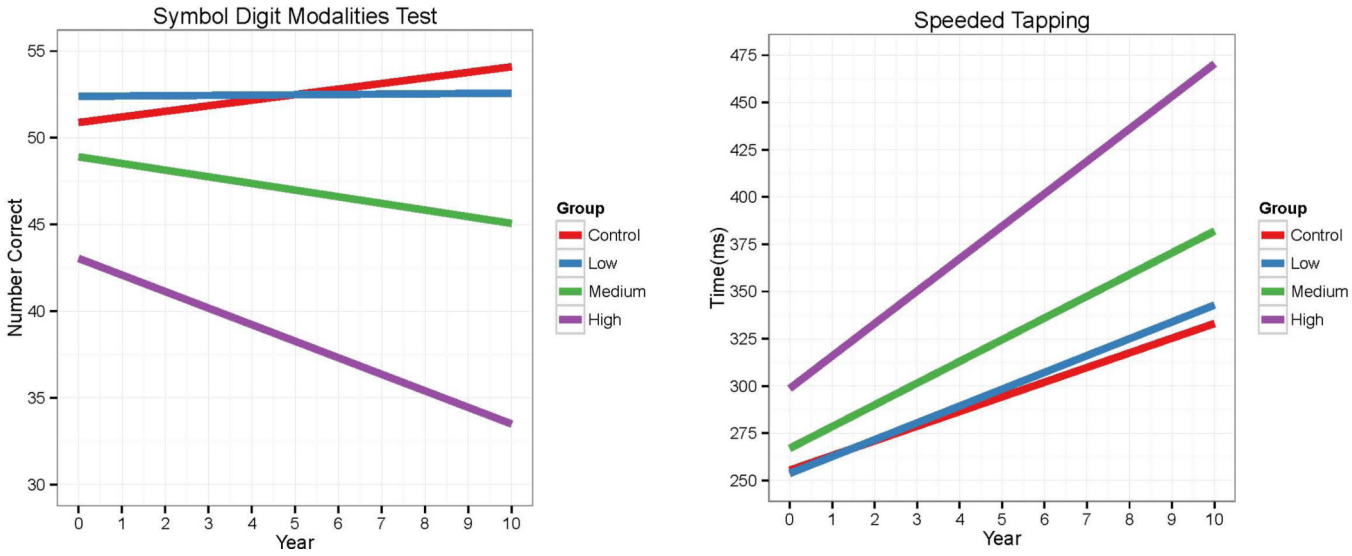

Figure 1.

The left-hand graph shows the fitted curves (based on a linear mixed effects regression fitted model) of the Symbol Digit Modalities Test by year for progression groups (Control, Low probability of near-future diagnosis, Medium probability, High probability; see Zhang et al.[6]). The right-hand graph shows the fitted curves for speeded tapping.

Reproduced from *Journal of Neurology, Neurosurgery & Psychiatry*, Paulsen JS, Smith MM, Long JD, PREDICT-HD Investigators and Coordinators of the Huntington Study Group, 84, 1233–1239, 2013, with permission from BMJ Publishing Group Ltd.

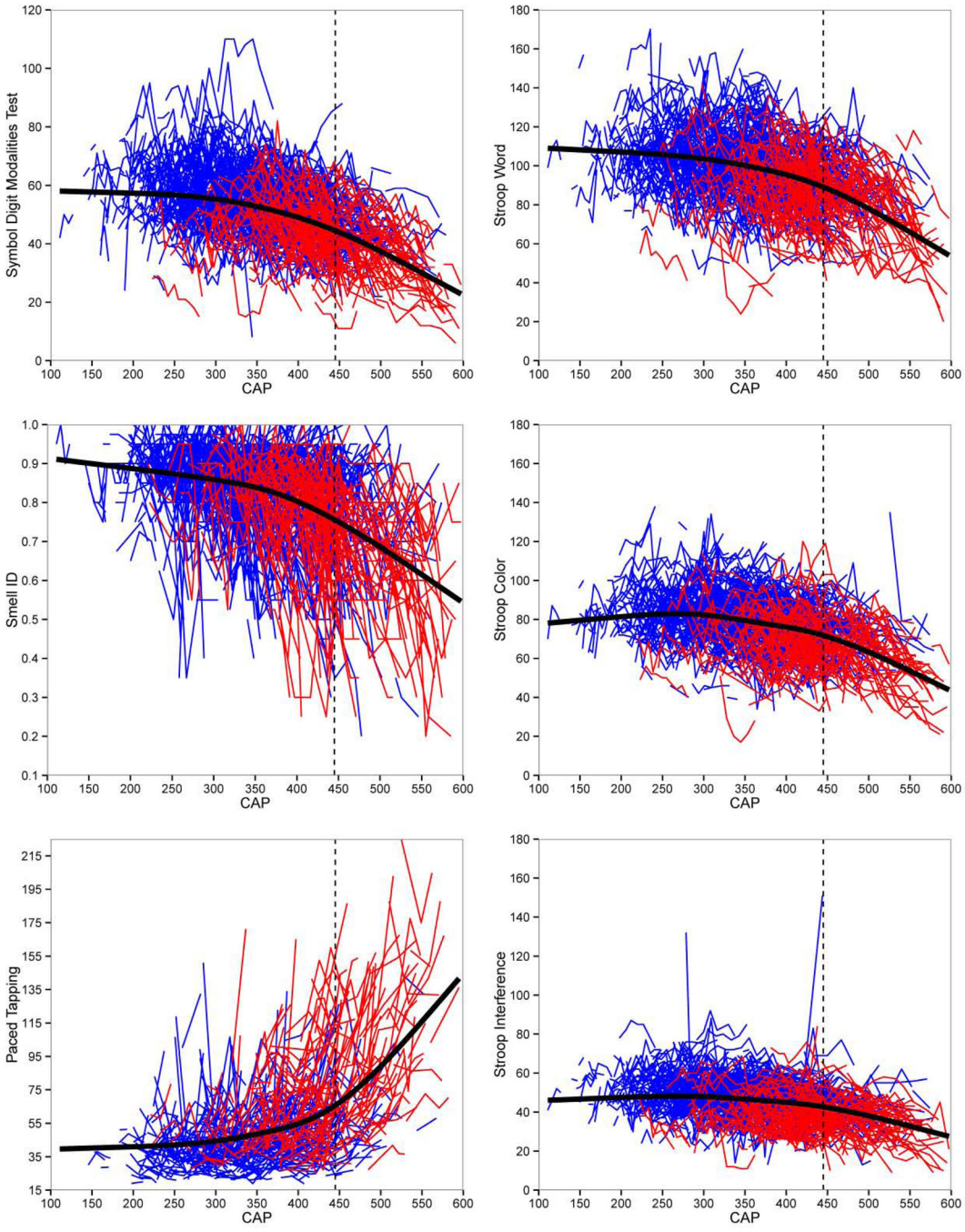

Figure 2.

Individual empirical curves (thin lines) and fitted cubic spline curves (thick lines) of cognitive variables by CAG-Age Product (CAP). Red lines indicate those who converted to a motor diagnosis over the course of the study (blue did not convert). The vertical dashed line indicates average CAP at diagnosis. CAP = Age × (CAG – 33.66) representing age adjusted for CAG expansion (see Zhang et al.[6]).

Abbreviations: Stroop Word, Stroop Color and Word Test – word condition; Smell ID, University of Pennsylvania Smell Identification Test (UPSIT); Stroop Color, Stroop Color

and Word Test – color condition; Stroop Interference, Stroop Color and Word Test – interference condition.

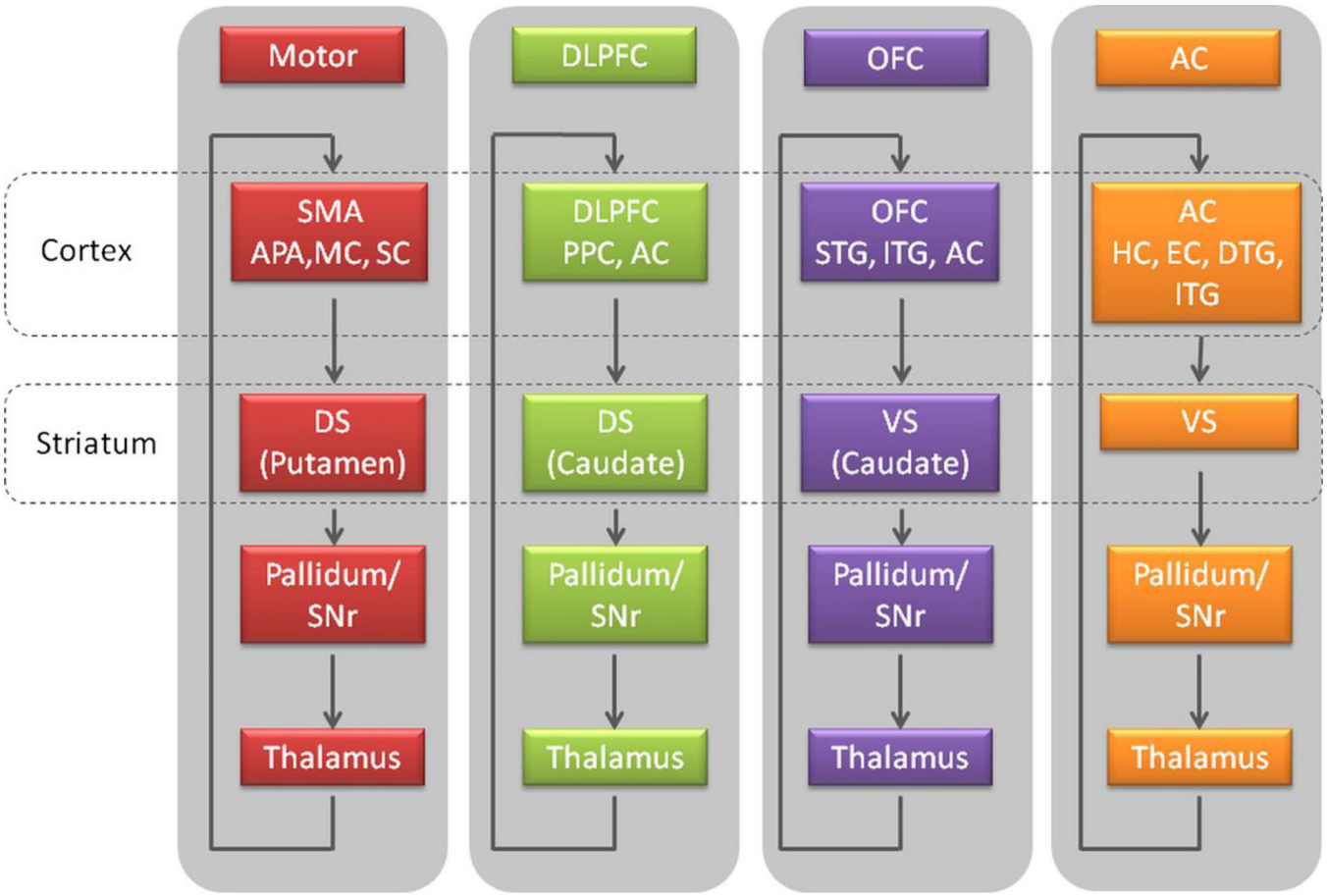

Figure 3.

Simplified representation of basal ganglia-thalamocortical circuits, adapted from Alexander et al.32 Each circuit engages specific regions of the cerebral cortex and striatum. Note, the figure does not take into account interconnectivity between striatal regions.

Abbreviations: AC, anterior cingulate area; APA, arcuate premotor area; DS, dorsal striatum; DLPFC, dorsolateral prefrontal cortex; EC, entorhinal cortex; HC, hippocampal cortex; ITG, inferior temporal gyrus; OFC, orbitofrontal cortex; MC, motor cortex; PPC, posterior parietal cortex; SC, somatosensory cortex; SMA, supplementary motor area; SNr, substantia nigra; STG, superior temporal gyrus; VS, ventral striatum. .

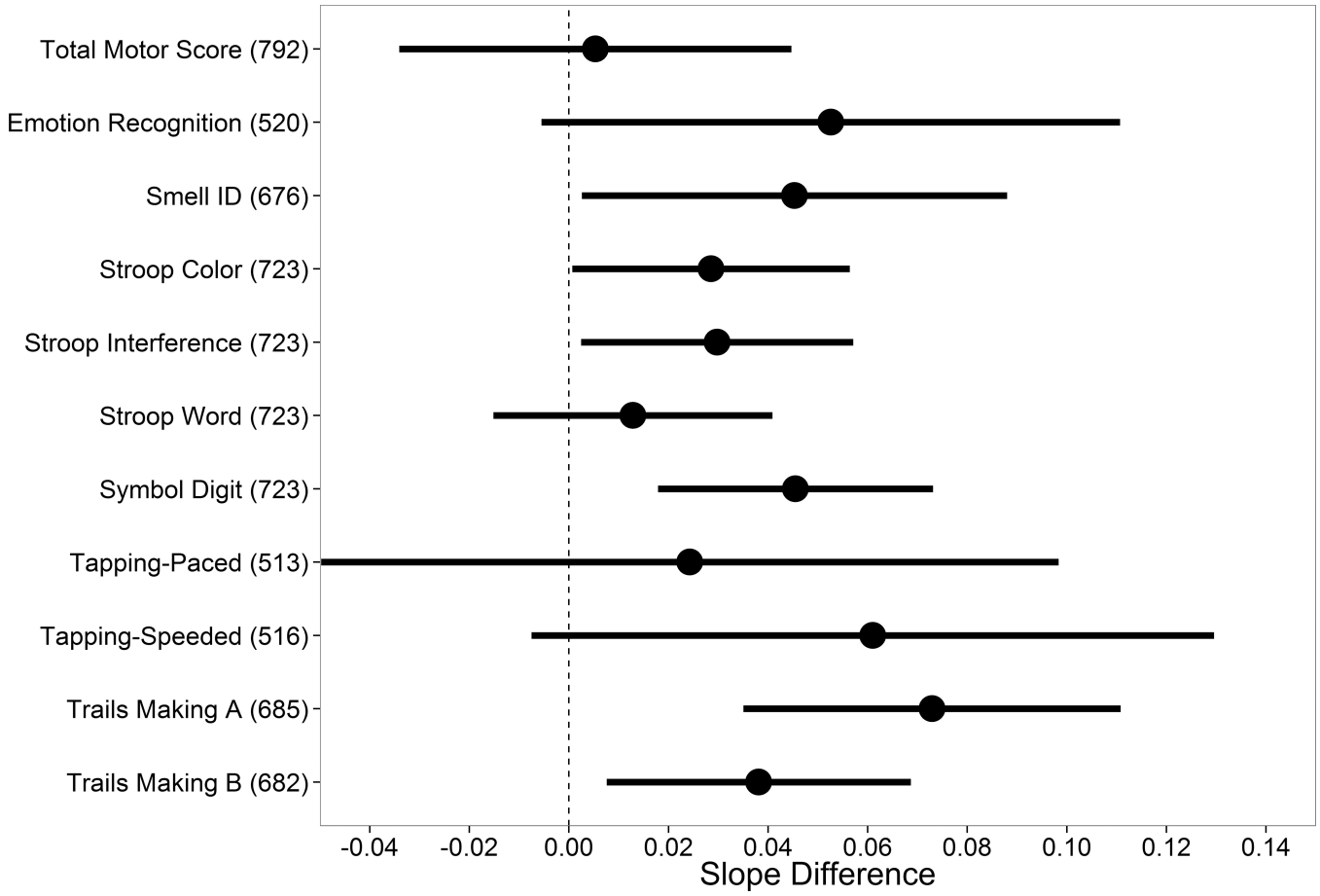

Figure 4.

Point estimates (circles) and 95% confidence intervals (lines) of standardized absolute value slope differences between cases and controls. Sample sizes are shown in parentheses. Abbreviations: Emotion recognition, emotion recognition test; Smell ID, University of Pennsylvania Smell Identification Test (UPSIT); Stroop Color, Stroop Color and Word Test – color condition; Stroop Interference, Stroop Color and Word Test – interference condition; Stroop Word, Stroop Color and Word Test – word condition; Symbol Digit, Symbol Digit Modalities Test; Trails Making Test A, Trail Making Test, Part A; Trails Making Test B, Trail Making Test, Part B.

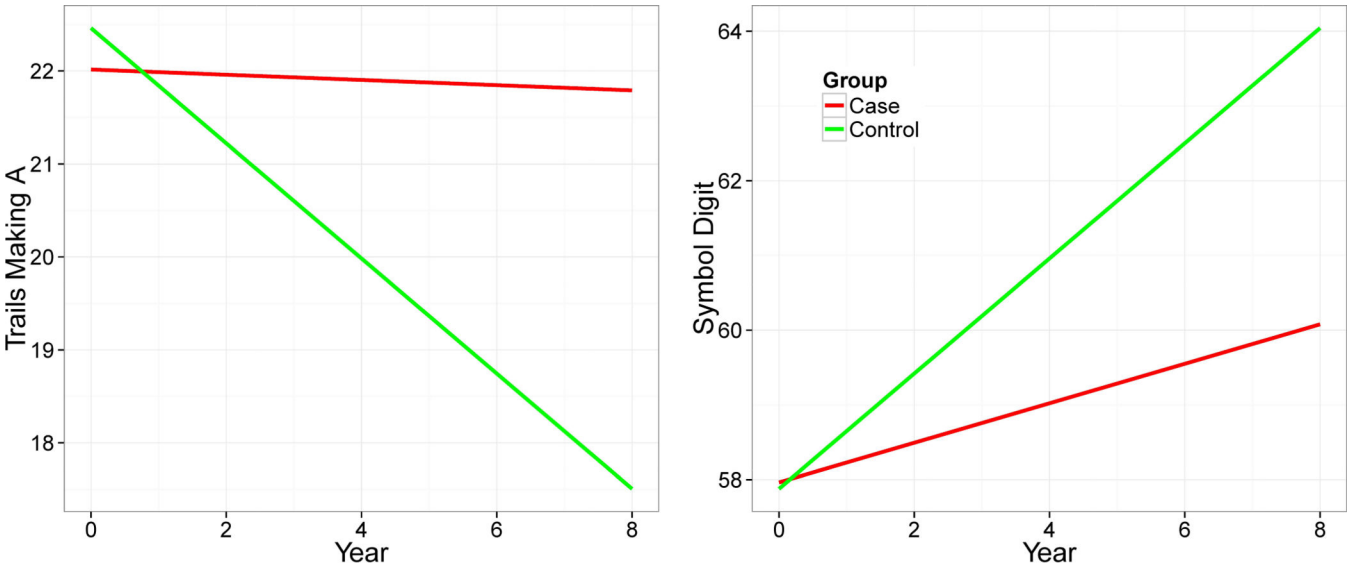

Figure 5.

Fitted longitudinal curves (controlling for covariates) of Trail Making Test, Part A (left) and Symbol Digit Modalities Test (right) by group. Raw scores are depicted.

Table 1

Cross-sectional effect size (Cohen's *d*) of cognitive variables in three prodromal HD groups (defined by Langbehn et al.[4]).

	Progression Group		
Variable	**Near**	**Mid**	**Far**
Symbol Digit Modalities Test[#]	−0.96***	−0.49***	−0.05
Stroop Color[#]	−0.75***	−0.39***	−0.11
Stroop Word[#]	−0.66***	−0.27*	0.03
Stroop Interference[#]	−0.62***	−0.32	0.03
Speeded Tapping[×]	−0.77***	−0.38***	−0.14
Paced Tapping[#]	−1.06***	−0.50***	−0.10
Smell ID[#]	−1.04***	−0.36**	−0.12
Trail Making Test-A[×]	−0.60***	−0.22	0.00
Trail Making Test-B[×]	−0.80***	−0.33**	−0.10
Emotions (static)[#]	−1.10***	−0.61***	−0.26

*** $p < .001$.

** $p < .01$.

[#] higher values indicate better performance.

[×] higher values indicate worse performance.

Abbreviations: Stroop Color, Stroop Color and Word Test – color condition; Stroop Word, Stroop Color and Word Test – word condition; Stroop Interference, Stroop Color and Word Test – interference condition; Smell ID, University of Pennsylvania Smell Identification Test (UPSIT); Trail Making Test-A, Trail Making Test, Part A; Trail Making Test-B, Trail Making Test, Part B; Emotions (static), emotion recognition test.

Table 2

Longitudinal results of cognitive change over time in three prodromal HD groups (defined by Zhang et al.[6]) compared to normal controls.

Variable	Slope Difference with Controls			Z-value of Difference		
	Low	Medium	High	Low	Medium	High
Symbol Digit Modalities Test#	−0.0386	−0.0780	−0.1405	−2.69	−5.96	−11.03
Stroop Color#	−0.0138	−0.0528	−0.1167	−0.96	−4.05	−9.20
Stroop Word#	−0.0257	−0.0427	−0.1110	−1.94	−3.54	−9.48
Stroop Interference#	−0.0280	−0.0407	−0.1027	−2.09	−3.33	−8.60
Speeded Tapping×	0.0355	0.1249	0.3157	0.76	2.97	7.74
Paced Tapping#	−0.0361	−0.0784	−0.1123	−1.62	−3.83	−5.65
Smell ID#	−0.0404	−0.0760	−0.1577	−1.89	−3.89	−8.15
Trail Making Test-A×	0.0622	0.0758	0.1960	2.15	2.89	7.62
Trail Making Test-B×	0.0671	0.0710	0.1871	2.42	2.81	7.59
Emotions (static)#	−0.0020	−0.0010	−0.0971	−0.07	−0.04	−3.69

The columns “Slope Difference with Controls” show the standardized difference between each progression group and the control group in SD units. The columns “*Z*−value of Difference” show the *Z*−ratio for each difference depicted in the previous columns. The *Z*−ratio is the effect size for a specific effect, and the shading indicates $|Z| > 2$.

#Higher values indicate better performance.

×Higher values indicate worse performance.

Abbreviations: Stroop Color, Stroop Color and Word Test – color condition; Stroop Word, Stroop Color and Word Test – word condition; Stroop Interference, Stroop Color and Word Test – interference condition; Smell ID, University of Pennsylvania Smell Identification Test (UPSIT); Trail Making Test-A, Trail Making Test, Part A; Trail Making Test-B, Trail Making Test, Part B; Emotions (static), emotion recognition test.

Reproduced from *Journal of Neurology, Neurosurgery & Psychiatry*, Paulsen JS, Smith MM, Long JD, PREDICT-HD Investigators and Coordinators of the Huntington Study Group, 84, 1233–1239, 2013, with permission from BMJ Publishing Group Ltd.

Mov Disord. Author manuscript; available in PMC 2015 September 15.

Table 3

Descriptive statistics of the sample in the data analysis. Percentage shown for a categorical variable and mean (standard deviation) shown for a quantitaive variable.

Group	*N*[a]	Female	Unblinded[b]	>1 Wave	Duration	CAG[c]	Age	Education
Case	559 (70.58%)	60.99%	81.03%	63.30%	2.89 (2.63)	42.11 (2.44)	38.77 (9.91)	14.63 (2.63)
Control	233 (29.42%)	66.38%	71.06%	74.89%	3.65 (2.57)	20.37 (3.61)	42.81 (11.33)	14.86 (2.67)

[a] Maximum sample size, see Figure 4.

[b] Percentage answering “Yes” to UHDRS item 81.

[c] cytosine-adenine-guanine expansion.