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The Trail Making Test in Prodromal Huntington Disease: Contributions of Disease Progression to Test Performance

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Abstract

We examined the Trail Making Test (TMT) in a sample of 767 participants with prodromal Huntington disease (prodromal HD) and 217 healthy comparisons to determine the contributions of motor, psychiatric, and cognitive changes to TMT scores. Eight traditional and derived TMT scores were also evaluated for their ability to differentiate prodromal participants closer to estimated age of diagnosis from those farther away and prodromal individuals from healthy comparisons. Results indicate that motor signs only mildly affected part A, and psychiatric symptoms did not affect either part. Tests of perceptual processing, visual scanning, and attention were primarily associated with part A, and executive functioning (response inhibition, set-shifting), processing speed, and working memory were associated with part B. Additionally, TMT scores differentiated between healthy comparisons and prodromal HD individuals as far as 9–15 years before estimated diagnosis. In participants manifesting prodromal motor signs and psychiatric symptoms, the TMT primarily measures cognition and is able to discriminate between groups based on health status and estimated time to diagnosis.

Keywords

Huntington disease; cognition; motor; psychiatric; neurodegenerative

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INTRODUCTION

Several studies have sought to identify the cognitive functions that underlie Trail Making Test (TMT; Reitan, 1958) performances, a widely used measure of cognitive-motor functioning. The TMT is given in two parts: part A, which requires the rapid connection of sequentially ordered numbers, and part B, which requires patients to connect alternating letters and numbers. In a healthy population, Sanchez-Cubillo and colleagues (2009) identified visuoperceptual abilities and visual search as the primary components of part A and working memory and speeded set-shifting for part B, indicating that part B emphasizes executive functioning in addition to visuoperceptual abilities. Other studies have also found that psychomotor speed (Crowe, 1998; Misdraji & Gass, 2009; Schear & Sato, 1989) and general intelligence (Lamberty, Putnam, Chatel, Bieliauskas, & Adams, 1994; Tremont, Hoffman, Scott, & Adams, 1998) can strongly correlate with TMT scores.

TMT performances are traditionally scored based on the time required to complete parts A and B of the test. The numbers of errors for each part are also frequently analyzed to provide additional clinical information. Derived scores that examine the relationship between part A and B have also been developed (e.g., time to complete part B – time to complete part A). Derived scores are thought to enhance the test's sensitivity to certain cognitive domains (e.g., executive functioning) while minimizing the influence of non-cognitive factors on TMT scores, such as psychiatric conditions and demographic variables, which can complicate the interpretation of TMT performance. For example, the most common psychiatric condition thought to influence TMT performance is depression (Austin et al., 1999; Hammar & Ardal, 2009; Porter, Gallagher, Thompson, & Young, 2003; Yaffe et al., 1999) because it leads to slower test completion times, most likely due to associated bradyphrenia and psychomotor slowing. Subtracting part A—the more direct measure of processing speed—from part B is thought to isolate the slowing effects of depression from the "executive" components of part B by removing the portion of the variance attributed to processing speed in part B scores. Other common confounding variables that are similarly minimized with derived scores include characteristics such as age (Coffey et al., 2001; Drane, Yuspeh, Huthwaite, & Klingler, 2002; Tombaugh, 2004) and education (Horton & Roberts, 2001a, 2001b, 2003; Saxton et al., 2000), especially with regard to part B.

Both traditional and derived TMT scores have been extensively used in populations suffering from a variety of neurological conditions, such as multiple sclerosis (Heaton et al., 1985), mild and severe traumatic brain injury (Rios, Perianez, & Munoz-Cespedes, 2004; Spikman, Kiers, Deelman, & van Zomeren, 2001), and Alzheimer disease (AD; Lamberty et al., 1994). Within the broader neurological literature, there have been investigations into the TMT's ability to detect the *prodromal* manifestations of neurodegenerative diseases. For example, a prospective case-control study (Chen et al., 2000) examined the ability of the TMT to detect cognitive dysfunction between those with presymptomatic AD and a healthy control group. The area under receiver operating characteristic (ROC) curves (AUC) demonstrated that TMT Part B was sensitive to group differences (AUC = 0.773), and when combined with a word list delayed recall task, was the most accurate method for discriminating normal comparisons from participants who eventually developed AD (AUC = 0.852). The sensitivity of the TMT to preclinical manifestations of AD implies that it may be a particularly useful measure for predicting the onset and course of disease in other neurodegenerative conditions before diagnosis.

Of interest in the present study is how the TMT is affected by the prodromal manifestation of another neurodegenerative condition and movement disorder, Huntington disease. Huntington disease (HD) is a fatal genetic disorder that results in a triad of psychiatric, motor, and cognitive impairments. Although impairments occur in multiple domains, an

individual is not usually diagnosed with HD until unequivocally manifesting an extrapyramidal movement disorder (Paulsen, 1999). Those who are found to have the HD gene-expansion (i.e., CAG repeat length) through genetic testing, but who do not yet exhibit significant motor signs, are said to be in the prodromal phase of HD (prodromal HD). Because the gene mutation is fully penetrant, individuals with prodromal HD will develop symptoms of HD with 100% certainty if they do not die of other causes first (Walker, 2007). Knowing the length of a person's CAG repeat expansion allows researchers to predict approximately when individuals with prodromal HD will exhibit motor signs that warrant an HD diagnosis (see Langbehn, Brinkman, Falush, Paulsen, & Hayden, 2004 and Langbehn, Hayden, & Paulsen, 2009 for details and validation of the Langbehn et al. formula).

The ability to identify those who will develop HD before they actually manifest symptoms and to approximate the onset of disease has enabled a number of studies to prospectively examine cognitive changes related to neuronal dysfunction in prodromal HD. Though many studies report that the TMT can distinguish prodromal HD individuals from neurologically normal individuals (Brandt, Shpritz, Codori, Margolis, & Rosenblatt, 2002; Foroud et al., 1995; Langbehn & Paulsen, 2007; Larsson, Almkvist, Luszcz, & Wahlin, 2008; Verny et al., 2007), no study has comprehensively examined the TMT in the prodromal phase of any movement disorder, let alone HD, in order to determine if the non-cognitive aspects of disease (psychiatric and motor dysfunction) are influencing TMT scores. If non-cognitive factors are influencing TMT scores, then neuropsychological interpretation of TMT scores must account for those factors when making inferences.

Since traditional and derived TMT scores have not been extensively studied in prodromal HD, it is unknown whether these scores are predominantly driven by motor, psychiatric, or cognitive changes in prodromal HD, which is an important question for a number of neuropsychiatric diseases. Biglan and colleagues (2009) found that individuals with prodromal HD manifest subtle motor signs as far as 9–15 years prior to estimated time of diagnosis. Such subtle changes in motor functioning could disrupt the essential graphomotor abilities necessary to complete the TMT. Similarly, psychiatric symptoms in prodromal HD (Duff, Paulsen, Beglinger, Langbehn, & Stout, 2007) could also potentially influence TMT performances. There has also been no investigation into how cognitive changes in prodromal HD influences TMT performances. Compared to healthy people, individuals with prodromal HD would likely have difficulties with the test because of disruptions in the frontal-subcortical circuitry. Interruption of the dorsolateral prefrontal circuit, due to changes in the basal ganglia, may be particularly relevant given the role of this circuit in organizing behavior and cognitive flexibility (Tekin & Cummings, 2002). Changes in subcortical frontal circuits have been observed well before any clinically detectible motor signs in prodromal HD (Aylward et al., 2004; Rosas et al., 2006).

Clinical trials of common neurocognitive enhancers, such as donepezil (Dichgans et al., 2008) and memantine (Bigal, Rapoport, Sheftell, Tepper, D., & Tepper, S., 2008), have used the TMT as an outcome measure with some success. These studies suggest that the TMT may be particularly useful as a primary outcome measure for clinical trials in prodromal HD. However, a greater understanding of the factors that contribute to TMT performance would be useful before considering it as a primary outcome measure in clinical trials of prodromal HD. There is a need to identify which of the traditional and derived scores are most sensitive to disease manifestation to inform selection of primary outcome measures and participant selection in studies evaluating the efficacy of clinical interventions.

The current study aimed to: (1) examine the contributions of prodromal HD signs and symptoms to TMT performances, and (2) identify potential TMT indices that warrant further examination for clinical trials. To address the first aim, we attempted to identify the

underlying contributions of psychiatric, motor, and cognitive symptoms to TMT performances in prodromal HD. The time to complete part A and part B were examined as the primary outcome variables because they are the primary scores of the test and are widely used among clinicians. We hypothesized that the cognitive aspects of prodromal HD would have the strongest associations with TMT performances. We also expected part A performances to correlate with measures of self-directed motor speed, sustained attention, and visuoperceptual processing. Part B scores were expected to correlate with tests of executive functioning and working memory. Motor functioning was expected to have a significant effect on completion times, but psychiatric symptoms were not. The second aim of this study was addressed through an evaluation of various TMT scores and their ability to differentiate prodromal HD participants closer to estimated time of diagnosis from those farther away, and prodromal HD individuals as a group from healthy comparisons.

METHOD

Participants

A total of 984 participants from the ongoing PREDICT-HD research project, a multi-site longitudinal examination of the neurobiological predictors of HD, took part in this investigation. Data were collected between September 2001 and April 2009 in order to prospectively identify clinical markers (i.e., cognitive, psychiatric, and motor) and biomarkers (i.e., neuroimaging, blood, and urine) of HD. All participants had a positive family history of HD and had undergone voluntary genetic testing prior to study enrollment. Patient-reported genetic test results were confirmed through blood draws obtained at their initial visit, and participants were subsequently classified into a gene-expanded group (prodromal HD; CAG repeat ≥ 36; n = 767) or a non-expanded healthy comparison group (HC; CAG repeat < 36; n = 217). The prodromal HD subsample was divided into three groups based on estimated proximity to diagnosis: NEAR (< 9 years; n = 183), MID (9–15 years; n = 287), and FAR (> 15 years; n = 297). Current age and CAG repeat length were used to estimate proximity to diagnosis according to a prediction formula developed by Langbehn and colleagues (2004).

Individuals were excluded from this study if they were younger than age 18 or had: (1) a history of a significant developmental cognitive disorder, (2) other CNS disease or injury, (3) evidence of an unstable medical or psychiatric illness, including alcohol or drug abuse, (4) a pacemaker or metallic implants, or (5) taken prescribed antipsychotic medication in the last six months or phenothiazine derivative antiemetic medication in the last three months. All participants underwent procedures approved by institutional review boards at their respective sites and provided informed consent for participation.

Procedure

All participants completed a clinician-administered demographic and medical questionnaire, a neuropsychological test battery, psychiatric assessments, and the Unified Huntington's Disease Rating Scale (UHDRS; Huntington Study Group 1996). All measures were administered by trained research technicians, with the exception of the motor assessment, which was conducted by certified motor raters blinded to gene status.

Measures

Demographic and Medical Questionnaire—Participants provided information about date of birth, gender, ethnicity, race, years of formal education, occupation, marital status, and handedness. Medical information about serious illnesses, allergies, psychiatric history, alcohol and substance abuse, and head injuries (including loss of consciousness) was also

collected. Participants also provided information about independent genetic testing, including the date of testing, test result, and CAG repeat length.

Neuropsychological Tests—The TMT is a two part paper-and-pencil test that requires participants to either connect consecutively numbered circles (TMT-A) or alternate between connecting consecutively numbered and lettered circles (TMT-B; Reitan & Wolfson, 1985). Both parts are to be completed as quickly as possible. The task is discontinued if the completion time exceeds 300 seconds on either part of the test. The number of errors for each part is also recorded.; therefore, none of the participants in our analysis met the discontinue criteria.

Derived scores are calculated using the completion times for both parts of the test. The difference between parts A and B (B − A) and the ratio of part B to A (B:A; Drane et al., 2002; Lamberty et al., 1994) are two of the more popular derived scores. The difference between B and A isolates the executive components of TMT-B (i.e., set-shifting, divided attention) by removing the psychomotor abilities measured by part A from part B (Heaton et al., 1985). The B:A ratio serves a similar purpose with the added advantage of being resistant to the influence of demographic factors, as demonstrated in neuropsychiatric conditions, traumatic brain injury, and Alzheimer disease (Lamberty et al., 1994). Other derived TMT indices that have been developed, but less extensively studied, include the sum (A + B) and the product (A × B/100) of part A and part B (Horton & Roberts, 2001a). Nonetheless, TMT sum and product scores may be clinically useful given their ability to differentiate between groups with varying degrees of neurological insult (i.e., brain injury; Lange, Iverson, Zakrzewski, Ethel-King, & Franzen, 2005).

The Symbol Digit Modalities Test (SDMT; Smith, 1991), Stroop Test (Stroop, 1935), and Wechsler Adult Intelligence Scale-III Letter Number Sequencing (L-N Sequencing; Wechsler, 1997) are examined as potential predictor variables of TMT performance because each test measures a cognitive-motor function that has been shown to influence TMT performance in healthy adults (e.g., Sanchez-Cubillo et al., 2009). The SDMT is a 90-second symbol-number transcription with raw scores ranging from 0–110. The Stroop Test consists of color reading, word reading, and interference trials each lasting 45 seconds. Raw scores are the number of correct responses within each trial. L-N Sequencing produces a scaled score (M = 10, SD = 10) and required participants to order and repeat alpha-numeric strings presented to them verbally. Higher scores indicate better functioning on all measures.

Psychiatric functioning—The Global Severity Index (GSI) of the Symptom Checklist-90-Revised (SCL-90-R; Derogatis, 1994) is utilized to examine the contribution of general psychological symptomatology on TMT performances. The SCL-90-R is a self-report measure that consists of 90 items in which participants rate their current level of discomfort from psychological symptoms on a 5-point scale (0 = *not at all* to 4 = e*xtremely*). The GSI is calculated by averaging the scores of all 90 items on the SCL-90-R, and higher scores indicate greater psychiatric distress. An unpublished factor analysis of the SCL-90-R has shown the GSI to be the scale's most psychometrically sound measure of general psychiatric problems in prodromal HD (D. R. Langbehn, personal communication, December 2009). The Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) is also used to directly assess depressive symptoms due to depression's possible association with psychomotor slowing. The BDI-II consists of 21 items, scored from 0 to 3, with higher scores indicating greater depression. BDI-II total scores range from 0–63.

Motor functioning—Motor functioning is assessed by trained motor raters using the Unified Huntington Disease Rating Scale (UHDRS) Motor Assessment (Huntington Study Group, 1996). The scale consists of 15 items that examine the motor signs of HD. Motor

examiners rate each item on a 5-point Likert scale (0 to 4), with higher total scores indicating greater motor dysfunction. Raters also provide an overall diagnostic impression to ensure participants' motor signs do not warrant a clinical diagnosis of HD. In the current study, the summed score from a subset of UHDRS items is individually examined to determine which aspects of visual (i.e., saccade initiation, saccade velocity, ocular pursuit) and limb (i.e., rigidity, chorea, dystonia, and alternating movements) motor variables in prodromal HD were related to TMT performance. A speeded finger tapping test is also used as a measure of self-directed manual motor skill. The non-dominant index finger is used to tap over five 10-second trials, and the average intertap interval in milliseconds is used as the raw score.

Statistical Analyses

Stepwise regression analyses were first employed to determine which cognitive (SDMT, L-N Sequencing, Stroop), psychiatric (SCL-90-R GSI, BDI-II), and motor variables (speeded finger tapping, saccade initiation, saccade velocity, ocular pursuit, rigidity, chorea, dystonia, and alternating movements) were most predictive of time to complete both parts of the TMT. All of the cognitive, psychiatric, and motor predictor variables were examined concurrently in order to avoid suppressor effects that would occur if the other potential predictors were held constant. Covariates were defined a priori and included gender, age, and years of education. Age, gender, and education were entered in the first step as independent variables and all the other variables were entered together in a second step.

Four traditional TMT scores (i.e., completion times, errors) and 4 derived scores (i.e., TMT sum, difference, ratio, product) were individually examined as outcome variables in an analysis of prodromal HD and HC participants to determine each score's ability to detect differences in test performances. First, differences between the entire prodromal HD and HC samples were analyzed using Student's *t*-tests adjusted for age, education, and gender to compare mean TMT scores based on gene-status. Effect sizes (Cohen's *d*) were calculated to determine the relative magnitude of difference between the prodromal HD and HC groups for each TMT score. An effect size value of .2 was considered "small," .5 was considered "medium," and .8 was considered "large." We then conducted an overall analysis of variance with covariates (ANCOVA) across four groups, which included the three prodromal HD prognostic groups (i.e., NEAR, MID, FAR) and the HC group. The ANCOVA was followed up with planned contrasts testing for differences among prognostic groups and the HC group. Finally, the AUC was calculated using ROC curves to determine the ability of each TMT score to discriminate (1) prodromal HD cases from HC and (2) participants in the NEAR prognostic group to HC. The NEAR group was selected due to their higher probability of demonstrating measurable signs and symptoms of HD, characteristics that make them more likely to be targeted for clinical trial recruitment.

RESULTS

See Table 1 for descriptive statistics for healthy comparisons and each of the prognostic groups. Thirty-eight participants (30 prodromal HD, 8 HC) were removed prior to the analysis due to missing data. Data for another nine prodromal HD participants were removed because their Trail Making Test scores were identified as statistical outliers. Of the nine participants, two met the 300 second discontinue criteria on TMT-B. Overall, there were no significant differences in gender or handedness between the groups (gender df = 3, $\chi^2 = 5.35$, $p = .15$; handedness df = 6, $\chi^2 = 7.28$, $p = .30$). Additionally, there were no significant differences in education when HC were compared to the prodromal HD group as a whole ($F_{3, 980} = 1.82$, $p = .142$); however, significant differences in education were found between the NEAR group and NC ($t = 2.26$, $p < .05$), with the NEAR group having slightly fewer years of education. Participants with prodromal HD were younger than HC (age

$F_{3, 980} = 32.74$, $p < .0001$). As would be expected, planned comparisons revealed significant age differences among all three prognostic groups, with younger participants being farther from diagnosis. When each prognostic group was compared to HC, the FAR group was the only group to differ in age ($t = 7.91$, $p < .0001$), and they were younger. There was no evidence of an interaction effect between demographic variables and group.

Stepwise regression results are presented in Table 2. Psychiatric signs of prodromal HD were not significantly related to TMT scores when entered into the stepwise regression analysis with the cognitive and motor variables. The stepwise multiple regression for part A was significant ($F_{6, 949} = 69.4$, $p < .0001$, model $R^2_{adjusted} = .31$), with SDMT (partial $R^2 = .12$), Stroop Word Reading (partial $R^2 = .032$), and speeded tapping (partial $R^2 = .013$) being the only variables retained. There was also a significant effect of age on part A performance (older individuals performed more slowly), but no gender or education effects. Cognitive measures were the only predictor variables related to part B. The overall stepwise regression was significant ($F_{7, 939} = 93.4$, $p < .0001$, model $R^2_{adjusted} = .41$), with SDMT (partial $R^2 = .13$), L-N Sequencing (partial $R^2 = .05$), Stroop Color Naming (partial $R^2 = .01$), and Stroop Interference (partial $R^2 = .01$) retained as predictor variables. In contrast to part A, only education had an effect on part B performance with more education being associated with faster part B completion times.

Independent *t*-tests comparing all prodromal HD cases with the HC showed that most TMT scores differentiated between the two groups (see Table 4). The only score that did not reveal a difference was part A Errors ($t = 1.52$, $p = .13$). The largest effect sizes observed between prodromal HD and HC were on TMT-Sum ($t = 4.32$, $p < .0001$, Cohen's $d = .34$), part B Time ($t = 4.17$, $p < .0001$, Cohen's $d = .33$), and TMT-Product ($t = 3.79$, $p < .001$, $d = .30$). The remaining TMT scores revealed significant, but smaller, effect sizes between prodromal HD and HC.

Table 3 summarizes the results from the ANCOVA, which tested the main effect of group (HC, FAR, MID, and NEAR) for each of the TMT measures and planned comparisons wherein each prodromal HD prognostic group was compared with the HC group. There was a main effect of group for all TMT scores except for part A Errors ($F_{6, 975} = 1.64$, $p = .13$, model $R^2_{adjusted} = .004$). There was evidence of an association between age (partial $R^2 = .006$ to .016, ps $< .0001$ to .015) and education (partial $R^2 = .002$ to .056, ps $< .0001$ to .0007) with part A (time) and part B (time and errors). Similarly, there was evidence of association between years of education with each of the four derived TMT scores (partial $R^2 = .029$ to .052, ps $< .0001$). Age was also associated with TMT-Difference, TMT-Product, and TMT-Sum, but not TMT-Ratio (partial $R^2 = .009$ to .019, ps $< .0001$ to .0028). These findings indicate that the majority of TMT indices were affected by age and education demographic variables in addition to gene status.

Planned comparisons revealed that the following TMT scores detected differences between the NEAR, MID, and FAR groups: part A Time, part B Time, TMT-Difference, TMT-Sum, and TMT-Product. It was notable that no TMT score significantly differentiated between the FAR and NC groups. Other TMT scores were sensitive to some group differences, but did not distinguish between all three prognostic groups. Of the TMT scores that were sensitive to prodromal HD group differences, TMT-Sum (NEAR vs. MID $d = .39$, $p < .0001$; MID vs. FAR $d = .39$, $p < .0001$; NEAR vs. FAR $d = .80$, $p < .0001$) and TMT-Product (NEAR vs. MID $d = .38$, $p < .0001$; MID vs. FAR $d = .41$, $p < .0001$; NEAR vs. FAR $d = .79$, $p < .0001$) produced the largest effect sizes between prognostic groups, followed by part B Time (NEAR vs. MID $d = .37$, $p < .0001$; MID vs. FAR $d = .34$, $p < .001$; NEAR vs. FAR $d = .73$, $p < .0001$).

When comparing the entire prodromal HD sample to HC, TMT-B, TMT-Sum, and TMT-Product were the most sensitive to group differences and nearly identical in their ability to discriminate between the groups (AUC = .634, .638, and .633, respectively). TMT-A, TMT-B Errors, and TMT-Difference were also similar to each other and not noticeably different from the previously mentioned scores (AUC = .621, .623, and .623, respectively). The scores proved more sensitive when discriminating between the NEAR group and HC. Again, TMT-B, TMT-Sum, and TMT-Product were similar, but the AUC for each measure improved to .717, .722, and .719 when examining the NEAR group alone. TMT-A, TMT-B Errors, and TMT-Difference also improved, but to a lesser degree (AUC = .691, .654, and .689).

DISCUSSION

The first goal of our study was to determine which aspects of cognitive, motor, and psychiatric functions were associated with TMT performance in prodromal HD. Our results demonstrated that the TMT primarily measures cognitive changes in prodromal HD and is not unduly affected by soft clinical motor signs or psychiatric aspects of disease manifestation prior to diagnosis. Consistent with our predictions and previous reports (Crowe, 1998; Sanchez-Cubillo et al., 2009), we found that part A primarily measures visual search and sustained attention, and part B taps cognitive flexibility and working memory. TMT-A performance was also related to self-directed manual motor speed (i.e., speeded tapping); however, the portion of the variance it accounted for was small compared to that of speeded visuoperceptual processing and scanning. Interestingly, the association of the SDMT with both parts A and B suggests that speed of perceptual processing and visual search are major components of both parts of the TMT, including the more "executive" part B. Prodromal changes in the occipital cortex may explain changes in visual search and perceptual processing. Lange (1981) found that patients diagnosed with HD exhibited the greatest cortical atrophy in the occipital lobe, with Brodmann areas 18 and 19 demonstrating a 30% reduction in volume compared to healthy patients. Rosas et al. (2008) also found that the superior occipital region was reduced in HD, and inversely correlated with performances on the Stroop and SDMT. Therefore, given our findings, it is possible that prodromal degeneration occurs in the occipital lobes long before diagnosis in a manner similar to what has been observed in the basal ganglia (Aylward et al., 2004).

Interestingly, cognitive variables only accounted for a portion of the variance in TMT scores (partial R^2 ranged from .01 to .13 across cognitive tasks). It may be that the remaining variance is accounted for by small contributions from a general intelligence factor that was not assessed by the independent variables in our study. Undetectable changes in fine motor functioning may also influence TMT performances. A previous study from our group found that bradykinesia had weak, but consistent, relationships with TMT-A, TMT-B, and TMT Difference (partial R^2 = .05 to .08, *p*s < .0001; O'Rourke et al., 2009). The relationship between speeded tapping and TMT-A performance in the current study may reflect the effects of early bradykinesia; although, this relationship was not present with part B, likely due to the enhanced cognitive demands of the test.

Our findings indicate that the motor and psychiatric aspects of prodromal HD did not significantly contribute to the variance in part B scores. There are a number of potential explanations for why motor changes did not appear to affect part B completion times. First, motor symptoms in prodromal HD are minimal. Biglan and colleagues (2009) found that prodromal HD participants had a mean UHDRS total motor score of 4.98 (+/− 5.23; total score ranging from 0 to 124, higher scores being worse), which was primarily accounted for by participants close to diagnosis. Even participants close to diagnosis (i.e., < 9 years) in their study had minimal motor signs with a mean UHDRS motor score of 7.80 (+/− 6.74).

Another possible explanation is that the added demands on executive functioning required by part B may negate individual differences in motor speed. Part A relies on rote memory for numbers; therefore, the cognitive demands of the test are small enough to minimize the confounding effect of cognition on motor speed. In contrast, shifting between numbers and letters, maintaining numerical and alphabetical order, and minimizing errors all require that participants approach part B more slowly and deliberately because of the increased cognitive burden, thus reducing the effect of motor speed on test performance.

Consistent with our prediction, general psychiatric functioning did not affect performances on either part A or B. Other studies have also reported a limited relationship between neurobehavioral symptoms and the TMT (e.g., Misdraji & Gass, 2009), although some suggest that depression slows performances significantly on both parts of the test (e.g., Gohier et al., 2009). Although we did not find a significant effect, this finding should be interpreted with some degree of caution given the psychological characteristics of the sample. Research on persons who have completed prodromal HD genetic testing suggests that there is a strong self-selection bias among these individuals. Individuals who choose to undergo genetic testing are a minority, and they tend to be socially extroverted, have high levels of social support, and lower levels of affective disturbance (Decruyenaere et al., 1995). As such, the limited degree of psychiatric disturbances in our sample is similar to what can expected in future prodromal HD studies, but it may not be reflective of the substantial majority of prodromal HD individuals who do not undergo genetic testing. Furthermore, the psychiatric measures used in this study may have also been affected by reduced insight, which has been found in HD populations (Hoth et al., 2007). The self-report nature of the measures makes them particularly susceptible to inaccurate self-perception.

The second goal of our study was to also examine the ability of TMT traditional and derived scores to detect prodromal HD group differences based on estimated proximity to diagnosis using the Langbehn et al. (2004) formula. Our cross-sectional results showed that both of the traditional TMT completion time scores distinguished between prodromal HD cases and HC individuals. These scores also differentiated between the three prodromal HD prognostic groups (i.e., NEAR, MID, and FAR); however, no score distinguished the FAR group from participants with the normal gene. The finding that traditional TMT completion time scores detect prodromal HD changes long before diagnosis is consistent with what has been reported for other subcortical movement disorders such as Parkinson disease (PD). For instance, Caviness and colleagues (2007) found that part B distinguished between cognitively normal PD patients and those who manifested signs of both amnestic and non-amnestic MCI. In addition to TMT completion times, we also found that participants with prodromal HD had a greater number of errors on part B than HC participants, which coincides with what has been found in patients with frontal lobe damage (Stuss et al., 2001) and indicates that frontostriatal dysfunction in prodromal HD may be partially responsible for these group differences. However, while errors on part B were useful for detecting overall differences between individuals with prodromal HD and HC, they did not distinguish between the NEAR, MID, and FAR prodromal HD groups. A lack of variance likely accounts for the inability of TMT error scores to distinguish between groups since the majority of prodromal HD cases and normal comparisons made no errors on part A (prodromal HD = 80%, NC = 85%) or part B (prodromal HD = 67%; NC = 80%). With regard to derived TMT scores, only TMT-Sum, TMT-Difference, and TMT-Product differentiated the prodromal HD and NC groups, as well as all three prognostic groups. Similar to the direct scores, no index differentiated the FAR group from normal comparisons.

We also examined the magnitude of effect sizes and the AUC for ROC curves on traditional and derived TMT scores between the entire prodromal HD sample (i.e., all three prognostic

groups collapsed into one group) and HC, and NEAR and HC, to assess the possibility of employing the TMT as a neurocognitive marker in prodromal HD. Effect sizes for significant group effects were small when comparing the entire prodromal HD sample to HC (ranging from d = .28 to .34). TMT-Sum and TMT-Product produced the largest effect sizes for between-group differences when compared to the other scores, likely due to increased variability in scores. The ROC curve analysis yielded similar findings, but demonstrated that TMT-B, TMT-Sum, and TMT-Product were most useful for discriminating those in the NEAR group from HC.

Ultimately, group comparisons and ROC curve analyses indicated that the larger effect sizes produced by derived scores were not of a sufficient magnitude to supplant the use of the traditional TMT scores for clinical purposes or drug trials in a prodromal HD population. Although the sensitivity of traditional scores was slightly less than TMT-Sum or Product, they have the advantage of well established norms and they are simpler to calculate. Traditional TMT scores may be excellent candidates for clinical trials aimed at slowing cognitive decline in prodromal HD, especially part B. Indeed, traditional TMT measures are widely used in clinical trials of pharmacological compounds. A recent study of donepezil in patients with subcortical vascular disease found that the time to complete TMT-A and TMT-B was the most sensitive measure to cognitive change, even beyond the study's primary cognitive assessment that was designed specifically for vascular disease populations (Dichgans et al., 2008). Other studies have used traditional TMT scores to study the effects of cognitive enhancers in migraine (e.g., Bigal et al., 2008) and schizophrenia patients (Fagerlund, Soholm, Fink-Jensen, Lublin, & Glenthoj, 2007) with similar results. Longitudinal studies are necessary to fully confirm the utility of TMT scores in clinical trials, and our findings lay the foundation for further investigation.

A shortcoming of the present study includes the limited prospective validation for the estimates we used to categorize prodromal HD participants into the three prognostic groups. Longitudinal analyses of the PREDICT-HD sample are necessary to fully establish the accuracy of the Langbehn et al. (2004) formula for predicting the onset of disease. Such validation may not be immediately available, especially for participants with prodromal HD in the FAR group who are estimated to be 15 years or more from diagnosis. Continued longitudinal analyses of individuals in PREDICT-HD who convert to diagnosed HD would also extend the present cross-sectional findings by refining our understanding of which TMT characteristics are most sensitive to the approaching onset of diagnosis. Lastly, our findings may have minimized the effect of motor symptoms on TMT performances because of our use of the UHDRS motor score in the analysis. The UHDRS was designed to detect and diagnose those with manifest HD, and therefore it may be less sensitive to any subtle motor changes in prodromal HD. Perhaps a more sensitive and objective measure designed for use in prodromal HD would better account for prodromal motor changes occurring far from diagnosis. Similarly, our findings cannot be assumed to generalize to those with a clinical diagnosis of HD. Observable motor signs are relatively subtle in prodromal HD when compared to their manifest HD counterparts (Biglan et al., 2009). We would expect that the significant motor dysfunction in manifest HD would confound the TMT's ability to assess cognition, given the prominence of positive motor signs (e.g., chorea, motor impersistence) in early HD (Mahant, McCusker, Byth, & Graham, 2003; Penney et al., 1990).

Summary

In prodromal HD participants manifesting prodromal motor signs and psychiatric symptoms, the TMT primarily measures cognitive abilities and does not appear to be significantly confounded by other aspects of prodromal HD. Furthermore, the TMT was able to discriminate between participants based on gene-status and estimated proximity to diagnosis. These results suggest that the TMT may be particularly useful as a cognitive

measure in the prodromal phase of movement disorders and other neurodegenerative diseases. Identifying cognitive measures that can be effectively coupled with psychiatric, motor, and neuroimaging markers will ultimately be necessary for preventive clinical trials in prodromal HD.

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TABLE 1

Descriptive statistics of demographics and predictor variables for healthy comparisons and prodromal Huntington disease prognostic groups [a]

Characteristic	Healthy comparisons	Prodromal Huntington Disease [b]		
		Far	Mid	Near
N	217	297	287	183
Gender (percent female)	66%	68%	62%	58%
Handedness (percent right-handed)	88%	89%	90%	87%
Age	43.7 (11.6) *19.2–83.7*	36.8 (8.05) *20.1 – 58.8*	42.3 (9.68) *26.1–72.9*	44.5 (10.2) *18.1–75.9*
Education	14.7 (2.69) *8–20*	14.4 (2.48) *8 – 20*	14.3 (2.82) *8–20*	14.1 (2.71) *8–20*
UHDRS Total Motor Score	2.6 (3.24) *0–22*	3.3 (3.66) *0–23*	4.6 (4.72) *0–25*	7.8 (6.43) *0–34*
Total Functional Capacity	13.0 (0.14) *12–13*	12.9 (0.53) *8–13*	12.8 (0.70) *7–13*	12.8 (0.71) *7–13*
Beck Depression Inventory-II	4.5 (5.21) *0–32*	7.9 (8.49) *0–46*	9.3 (9.53) *0–47*	6.7 (8.20) *0–48*
Symptom Checklist 90-Revised: Global Severity Index	0.29 (0.26) *0–1.82*	0.45 (0.45) *0–2.22*	0.48 (0.49) *0–2.91*	0.38 (0.40) *0–2.32*
Symbol Digit Modalities Test	53.8 (8.85) *26–83*	54.8 (11.2) *28–92*	49.5 (9.96) 25–76	44.0 (11.0) *18–72*
Stroop Color Naming	81.7 (12.6) *50–146*	81.2 (13.8) *44–130*	76.6 (13.4) *36–110*	71.7 (13.9) *36–135*
Stroop Word Reading	102.9 (14.7) *68–151*	103.4 (17.3) *44–155*	98.1 (16.9) *38–150*	91.9 (16.1) *48–130*
Stroop Interference	46.6 (9.61) *20–89*	47.9 (10.4) *19–82*	43.5 (9.53) *13–73*	40.4 (8.79) *17–69*
Wechsler Adult Intelligence Scale–III: Letter Number Sequencing	12.5 (3.12) *(6–21)*	12.2 (2.71) *6–21*	11.4 (2.78) *2–18*	10.9 (2.69) *4–20*
Speeded Finger Tapping[c]	232.3 (32.0) *147.9–390.7*	236.8 (37.9) *169.3–489.5*	249.3 (49.3) *161.5–488.1*	281.3 (68.3) *171.7–581.6*

[a] Descriptive statistics are presented as Mean(SD) with score ranges in italics below;

[b] NEAR ≤ 9 years from diagnosis, MID = 9–15 years from diagnosis, FAR ≥ 15 years from diagnosis;

[c] inter-tap intervals in milliseconds

TABLE 2

Summary of stepwise regression analyses for cognitive variables predicting performance on the Trail Making Test.

Outcome Variable	Variables	B	SE B	β	*p*-value
TMT-A Time (seconds)	Covariates				
	Gender	−.53	.56	−.03	.35
	Age	.08	.03	.09	.002
	Education	.07	.10	.02	.46
	Predictors				
	Speeded Tapping	.02	.01	.11	.0005
	SDMT	−.32	.03	−.37	<.0001
	Stroop Word	−.10	.02	−.18	<.0001
TMT-B Time (seconds)	Covariates				
	Gender	−1.39	1.60	−.02	.38
	Age	.14	.08	.05	.08
	Education	−.61	.30	−.05	.04
	Predictors				
	SDMT	−1.02	.09	−.37	<.0001
	Stroop Color	−.24	.08	−.11	.0018
	Stroop Interference	−.28	.11	−.10	.0094
	L-N Sequencing	−1.98	.30	−.19	<.0001

TABLE 3

ANCOVA testing group differences (HC, Far, Mid, Near) on each of the Trail Making Test (TMT) indices.

TMT Index	*F*-ratio for Overall ANCOVA (HC[1] and Far, Mid, and Near prHD[2] groups)	Prognostic Group[3] Means (SD)			
		HC[1]	Far	Mid	Near
A Time	17.43*	25.4 (8.6) *c,d*	24.2 (8.0) *c,d*	28.0 (9.3) *a,b,d*	31.3 (11.3) *a,b,c*
B Time	28.63*	59.3 (24.9) *c,d*	58.0 (24.6) *c,d*	69.1 (29.7) *a,b,d*	82.0 (36.0) *a,b,c*
A Error	1.64	.152 (.37) *d*	.209 (.46)	.195 (.47)	.257 (.57) *a*
B Error	9.78*	.270 (.61) *c,d*	.340 (.68) *d*	.484 (.89) *a,d*	.665 (.98) *a,b,c*
B − A	21.18*	33.9 (21.5) *c,d*	33.8 (22.6) *c,d*	41.1 (26.2) *a,b,d*	50.6 (30.7) *a,b,c*
A + B	30.98*	84.7 (30.4) *c,d*	82.3 (28.8) *c,d*	97.0 (35.3) *a,b,d*	113.3 (43.7) *a,b,c*
B:A	6.64*	2.41 (.84)	2.50 (.10)	2.55 (.98)	2.70 (.95) *a,b*
(A × B)/100	25.85*	16.2 (12.1) *c,d*	14.9 (9.9) *c,d*	20.7 (15.0) *a,b,d*	28.1 (21.5) *a,b,c*

[1] HC = healthy comparisons;

[2] prHD = prodromal Huntington disease;

[3] NEAR ≤ 9 years, MID = 9–15 years, FAR ≥ 15 years;

a Different from healthy comparisons;

b Different from FAR;

c Different from MID;

d Different from NEAR

* $p < .0001$

TABLE 4

Comparison of Trail Making Test (TMT) scores between healthy comparison and all prodromal Huntington Disease participants

TMT Index	HC[a] Mean (SD)	prHD[b] Mean (SD)	*t*	*d*[c]
TMT-A Time	25.4 (8.6)	27.3 (9.7)	3.14*	.244
TMT-B Time	59.3 (24.9)	67.9 (30.9)	4.17***	.325
TMT-A Errors	.152 (.37)	.215 (.49)	1.52	.118
TMT-B Errors	.270 (.61)	.471 (.85)	3.59**	.280
B − A	33.9 (21.5)	40.5 (26.8)	3.60**	.280
A + B	84.7 (30.4)	95.2 (37.2)	4.32***	.336
B:A	2.41 (.84)	2.56 (.98)	2.00 +	.156
(A × B)/100	16.2 (12.1)	20.2 (16.0)	3.79**	.295

[a] HC = healthy comparisons;

[b] prHD = prodromal Huntington disease;

[c] effect sizes are adjusted for age, education, and gender

*** $p < .0001$,

** $p < .001$,

* $p < .01$,

+ $p < .05$