Everyday Cognition in Prodromal Huntington Disease

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Abstract

Objective—Assessment of daily functions affected by cognitive loss in prodromal Huntington disease (HD) is necessary in practice and clinical trials. We evaluated baseline and longitudinal sensitivity of the Everyday Cognition (ECog) scales in prodromal HD and compared self- and companion-ratings.

Method—Everyday cognition was self-assessed by 850 participants with prodromal HD and 768 companions. We examined internal structure using confirmatory factor analysis (CFA) on baseline data. For longitudinal analysis, we stratified participants into Low, Medium, and High disease progression groups. We examined ECog scores for group differences and participant-and-companion differences using linear mixed effects regression (LMER). Comparison with the Total Functional Capacity (TFC) scale was made.

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Results—CFA revealed good fit of a 5-factor model having a global factor (total score), and sub factors (subscales) of memory, language, visuospatial perception, and executive function. At study entry, participants and companions in the Medium and High groups reported significantly worsened everyday cognition as well as significant functional decline over time. Losses became more pronounced and participant and companion ratings diverged as individuals progressed. TFC showed significant functional loss over time in the High group but not in the Medium group.

Conclusions—Disease progression is associated with reduced self- and companion-reported everyday cognition in prodromal HD participants who are less than 13 years to estimated motor onset. Our findings suggest companion ratings are more sensitive than participants' for detecting longitudinal change in daily cognitive function. ECog appears more sensitive to specific functional changes in the prodrome of HD than the TFC.

The ability to complete daily tasks is diminished in Huntington disease (HD), an autosomal dominantly inherited neurodegenerative disorder resulting from an expansion in cytosine, adenine and guanine (CAG) bases in the *HTT* gene (Huntington's Disease Collaborative Research Group, 1993). Cognitive, behavioral, and motor changes all occur in HD, with cognitive changes identifiable prior to motor onset (Beglinger et al., 2010; Biglan et al., 2013; Duff et al., 2010), which is the period of prodromal HD. Functional impairment increases in prodromal HD as motor diagnosis approaches (Muthén & Muthén, 1998–2010; Paulsen et al., 2006, 2008, 2010; Tabrizi et al., 2009, 2011, 2012), impacting daily living skills, work functions, and interpersonal relationships (Downing et al., 2013; Downing, Williams, Leserman, & Paulsen, 2012; Paulsen, 2010; Williams, Downing, Vaccarino, Guttman, & Paulsen, 2011). Assessment of daily function changes in prodromal HD is important for clinical monitoring and management, as well as for tracking functional capacity in clinical trials (Beglinger et al., 2010; Paulsen et al., 2010).

Previous work examining functional impairments in HD focused primarily on those who had already been given a motor diagnosis. Functional decline, as measured by the Total Functional Capacity (TFC) scale (Huntington Study Group, 1996), has been used widely in clinical trials as an outcome measure (Marder et al., 2000). Although motor impairments clearly lead to a variety of functional deficits (Brandt et al., 1984; Rothlind, Bylsma, Peyser, Folstein, & Brandt, 1993), many studies have shown cognitive and psychiatric impairments associated with HD significantly contribute to degree of functional impairment independent of motor impairments (Nehl, Paulsen, & Huntington Study Group, 2004). In particular, impairments in executive function have been associated with worsened activities of daily living (Hamilton et al., 2003). Additionally, greater degree of overall cognitive impairment has also been shown to predict rate of functional decline, such that those with greater cognitive impairment at study baseline show more rapid decline (Marder, et al., 2000).

Such findings are consistent with the wider literature examining the important role of cognitive function in the ability to do daily tasks in normal aging as well as in Alzheimer

disease (Benke et al., 2013; Martyr & Clare, 2012). Based on the finding that changes in everyday function can be observed in the prodromal stage of dementia – known as mild cognitive impairment (MCI) – it would be anticipated that functional changes likely accompany the very early cognitive changes occurring in prodromal HD. Indeed, recent research by our group demonstrates functional changes during the prodromal HD period (Downing et al., 2013; Paulsen et al., 2010).

One obstacle to studying early functional changes in HD has been limitation of assessment methods. Instruments such as the TFC (Huntington Study Group, 1996) appear to be sensitive to changes following a motor diagnosis of HD (Marder et al., 2000) but may not have sufficient sensitivity to changes during prodromal HD (Downing et al., 2013; Paulsen et al., 2010). Further, given that cognitive impairments are among the very first signs of HD to emerge, there is a need for new functional assessment tools that specifically target cognitively-based functional abilities.

Another issue relevant to measuring functional capacities in HD and prodromal HD is determining which method of ascertainment is most appropriate. Both companion and self-report of functional abilities have been used in HD and other populations. Due to the possibility of diminishing self-awareness as motor onset nears (Duff et al., 2010; Ho, Robbins, & Barker, 2006; Hoth et al., 2007), assessment from a companion may provide an important source of data. Discrepancies between participant and companion ratings in awareness of cognitive, behavioral and functional changes have been reported in those estimated to be closest to diagnosis (Downing et al., 2013; Duff et al., 2010).

To address some of the gaps in knowledge about the nature of very early functional changes in prodromal HD, the present study examines self- and companion-rated everyday cognition in prodromal HD and compares ratings with the widely-used TFC. The four study aims were: (a) Compare the factor structure of the Everyday Cognition (ECog) scales (Farias et al., 2008) in a sample of people with prodromal HD to the factor structure of the original ECog using baseline data; (b) analyze baseline and longitudinal changes in participant and companion ratings of the ECog by disease progression groups; (c) compare participant and companion ratings over time in each disease progression group; and (d) assess the sensitivity of the ECog by comparison to the TFC for detecting change over the prodromal phase of HD. We hypothesized that the factor structure in the revised ECog would be similar to the original ECog. We anticipated that both participants and companions would report functional changes over time. However, we expected that companion ratings would diverge from participant ratings as participants become nearer to the time of diagnosis, owing to diminishing self-awareness in the participant group. Lastly, we expected that the ECog would be more sensitive than the TFC in detecting specific domains of daily cognitive function.

Method

Participants

Participants were from the Neurobiological Predictors of Huntington's Disease (PREDICT-HD) study (Paulsen et al., 2006; Paulsen et al., 2008). PREDICT-HD participants were

independently tested for the CAG gene mutation before participation in the study. Individuals with the CAG repeat expansion (CAG ≥ 36) who did not receive a motor diagnosis of HD at study entry served as gene-expanded cases, whereas individuals without the CAG expansion (CAG < 36) served as controls (Table 1). The PREDICT-HD study began data collection in 2001 and a shortened version of the ECog scale was added to the battery in 2009 following analyses suggesting insensitivity of functional scales (Beglinger et al., 2010; Paulsen et al., 2010). This analysis includes data from $N = 850$ participants with 1911 observations, and $N = 768$ companions with 1596 observations collected over the time period of 2009–2012. Companions were predominantly spouse/partner (74%), followed by friend/neighbor (8%), parent (7%), and sibling (5%), and 75% of the companions reported living with the target participant. The mean number of years companions reported knowing the participants was 21.19 years ($SD = 14.07$). The median number of follow-up visits was two, with a range of one to four. The median length of follow-up was 1.37 years ($max = 3.11$ years).

Individuals entered PREDICT-HD with different baseline disease progression levels and were classified accordingly. In this analysis, baseline refers to the initial visit when the ECog was first administered for each participant. Participants were classified into one of three HD prodromal groups based on the CAG-Age Product (CAP) score (Zhang et al., 2011) computed as CAP = (age at entry) × (CAG − 33.66). CAP is a purported index of the cumulative toxicity of the huntingtin protein at time of study entry, and it is closely related to the "genetic burden" score developed earlier by Penney et al. (1997). As shown by Zhang et al. (2011), the estimated time to motor diagnosis from study entry for each gene-expanded group is > 12.8 years for the Low group, 7.6–12.8 years for the Medium group, and < 7.6 years for the High group. Four groups were used in this analysis: Control, Low, Medium, and High. Table 1 describes the demographic characteristic of the groups.

Functional Capacity Measures

The Everyday Cognition scales (ECog)—The original ECog included 39 items in six subscales: memory (eight questions), language (nine questions), visuospatial abilities (seven questions), planning (five questions), organization (six questions), and divided attention (four questions). In PREDICT-HD, the original ECog was shortened to reduce redundancy and subject burden. Five of the original items were removed, resulting in a 34 item measure. The items removed were: (1) thinking things through before acting; (2) thinking ahead (planning subscale); (3) keeping living and work space organized; (4) keeping financial records organized (organization subscale); and (5) returning to a task after being interrupted (divided attention subscale). One item on the original organization scale, balancing the checkbook without error, was moved into the divided attention subscale. Three items on the original organization scale, prioritizing tasks by importance, keeping mail and papers organized, and using an organized strategy to manage a medication schedule involving multiple medications, were moved into the planning subscale. The ECog used in the current analysis included items in five subscales: Memory (original eight questions), language (original nine questions), visuospatial perception abilities (original seven questions), planning (six questions: three original Planning and three original Organization), and divided attention (four questions: three original Divided Attention, and one original

Organization). The difference between the original ECog and our version is the manner in which the executive function items were organized. Our version classified 10 of the original 15 executive function items into two subscales–planning and divided attention–whereas the original ECog had three subscales that also included the omitted items.

Each ECog item had four response categories: 1 = no difficulty; 2 = mild-occasional difficulty; 3 = moderate – often has difficulty, 4 = severe difficulty, with higher scores indicating worse everyday function. The ECog total score was calculated as the mean of 34 items with a total possible range of scores 1–4. Four subscale scores (memory, language, visuospatial perception abilities, and executive function), were computed as the mean of the subscale items. Missing data were ignored by averaging over the available items, except when a single subscale had more than half of the items missing. In the latter case, the participant or companion was excluded from the analysis, which amounted to 3% of the data.

Total Functional Capacity

The TFC is a broad measure of functional capacity that is rated by a trained examiner after a brief interview with participants, with input allowed from their companions (Shoulson & Fahn, 1979). The TFC consists of five items assessing occupation, finances, domestic chores, activities of daily living (ADL), and care level. Each item has either three or four response categories (0 to either 2 or 3) for a total possible range of scores from 0–13, with higher scores indicating better functioning. A complete analysis of TFC in prodromal HD showed that three items (domestic chores, ADL, and care level) were endorsed by less than 2% of participants in PREDICT-HD 1.0 (Paulsen et al., 2010) and were thus excluded to reduce research burden. The two retained items were summed to yield a modified TFC score in this analysis. To facilitate comparison with the ECog, TFC was scaled as TFC loss, computed as 6 - (occupation item score + finances item score). Higher TFC scores indicate better functioning whereas higher ECog scores indicate worse functioning. By calculating a TFC loss score, higher scores indicate worse functioning for both loss of TFC and ECog. TFC loss scores range from 0–6, with higher score indicating worse functioning.

Statistical Methods

Confirmatory factor analysis of the ECog—The original ECog was developed using sample groups with normal cognition, MCI, and dementia. To compare the factor structure of the modified ECog in our prodromal HD sample with that of the original ECog, a confirmatory factor analysis (CFA) was performed using baseline ECog data. Following Farias et al. (2008), a bifactor model (Chen, West, & Sousa, 2006) was fit to the data. A bifactor model assumes that all the items are correlated through a single global factor, but there are domain-specific factors that account for additional unique variance apart from the global factor. Model fit was assessed by the comparative fit index (CFI) (Bentler, 1990), the root mean square error of approximation (RMSEA) (Steiger, 2000) and the Tucker-Lewis index (TLI) (Tucker & Lewis, 1973). The CFI and TLI range from 0–1 and values of 0.95 or higher indicate acceptable model fit (Hu & Bentler, 1999). RMSEA values less than 0.08 are considered indicative of adequate fit, and values less than 0.05 indicative of good fit (Browne, Cudeck, Bollen, & Long, 1993). Additional details are provided in Appendix A.1.

Five models were fitted: (a) a model with a single global factor; (b) a model with a global factor and two domain-specific factors–memory, and non-memory; (c) a model with a global factor and four domain-specific factors–memory, language, visuospatial abilities, and executive functions (planning, organization, and divided attention items were combined); (d) a model with a global factor and five domain specific factors– memory, language, visuospatial abilities, planning and divided attention; and (e) a model with a global factor and six domain specific factors–memory, language, visuospatial abilities, planning, organization and divided attention. Each model was compared to the one factor model by a modified chi-squared difference test (Asparouhov & Muthén, 2006). The analysis was performed in Mplus 6.0 (Muthén & Muthén, 1998–2010) and a mean and variance adjusted weighted least squares estimator (Muthén, du Toit, & Spisic, 1997) was used for all analyses.

Group comparison of baseline and longitudinal change—To test whether there were differences between the gene mutation-negative controls and each of the gene-expanded groups at baseline and in change over time, participant and companion ECog ratings were analyzed separately using linear mixed effects regression (LMER) (Pinheiro & Bates, 2000). We used all time points available for each subject in our LMER analysis. LMER is a flexible model which allows a different number of visits per participant, and can handle missing data that are missing at random. The time metric was years since initial ECog administration. All models included the covariates of age at entry, gender, and years of education. Three LMER models were fitted to test for a group difference at baseline or in longitudinal trajectories (slopes): Model 1 was a null model which included the covariates and duration as predictors, but no group differences; Model 2 added group main effects to test group baseline differences (group intercept effect); Model 3 added the interactions between duration and groups to test group differences in the rates of change over time (group slope effect). Additional details are provided in Appendix A.2. The models were evaluated by Akaike's information criterion (AIC) corrected for sample size (AICc) (Hurvich & Tsai, 1989). To rank the models, two scalings of AICc were computed: the difference in AICc (dAICc) and the AICc weight (wAICc) (Burnham & Anderson, 2002). The dAICc was computed as the difference in AICc values between each model and the model with the lowest AICc. Smaller dAICc values indicate better fit. The wAICc is a probability scaling (0 ≤ wAICc ≤ 1) with values closer to 1 indicating better fit. If Model 2 or 3 was best fitting, baseline and longitudinal differences between the controls and each of the gene expanded groups were reported. We also examined whether living with the participant had an influence on the companion's rating in separate analyses. An indicator variable, Living Together, and its interaction with time metric (Living Together × years since initial ECog administration) were included in the three models considered for each outcome, and three models were evaluated by AICc.

Participant and companion ECog comparison—To test for longitudinal differences between participant and companion ratings in each group, participant and companion ratings were modeled simultaneously using multi-response LMER models (Long, 2012). Details are provided in the Appendix (A.3). If there was no longitudinal difference between participant and companion ratings, participants and companions would have equal rates of change

(slope); if there was a discrepancy between participant and companion ratings, they would have unequal slopes. There were various combinations of equal and unequal slopes among the groups, resulting in 16 possible candidate models, as shown in the Appendix (Table A. 1). Model 1 was the simplest, having equal slopes in all groups; model 16 was the most complex, having unequal slopes in all groups. All models included age at entry, gender, and years of education as covariates. The relative importance of slope discrepancy in each group was computed as the sum of the AICc weights (wAICc) across all models with unequal group slopes (Burnham & Anderson, 2002). A sum closer to one indicates better fit. Fitted curves were drawn using model-averaged parameters over all models (Burnham & Anderson, 2002). Model-averaged parameters were computed by averaging model parameters over all models after multiplying the weight of the model and the estimated parameters for the given model.

ECog and TFC comparison—To assess the sensitivity of the ECog (i.e. participant ratings) in detecting changes in day-to-day function in prodromal HD, longitudinal change was indirectly compared with the TFC. Because TFC loss and ECog are measured in different units, both were transformed to a common scale by subtracting the mean from each measure and then dividing by the standard deviation. The mean and standard deviation for each measure were computed using data from all the time points. For each scaled variable, the model with baseline and longitudinal group effects was fitted. The effect size for a group was based on the difference in baseline and longitudinal differences between the controls and each of the gene-expanded groups. The effect sizes were the *t*-values of the differences, computed as the difference divided by its standard error. In each group, effect sizes were compared between ECog and TFC loss when the effect was significant for at least one measure.

Results

Factor Structure of the ECog Among a Prodromal HD Sample

Participant characteristics at the initial ECog administration are presented in Table 1. There were 197, 299, 300, and 54 participants with one, two, three, and four visits, respectively; there were 233, 273, 231, and 31 companions with one, two, three, and four visits, respectively.

Table 2 shows the results of four confirmatory factor models of ECog total scores at baseline. As the table shows, fit of the 1-Factor Model was relatively poor on all indexes except RMSEA (CFI=0.931, TLI=0.927, RMSEA=0.079). The result for the 3-Factor model was not shown since this model did not converge. In contrast, the 5, 6, and 7-Factor models did converge, and all had very similar model fits: all indices were indicative of good model fits (all CFIs and TLIs > 0.95, all RMSEAs < 0.05). All models also provided significantly better fit than the 1-Factor Model by modified chi-square difference tests (all *p*s < 0.001). Thus, we decided to use the most parsimonious model, the 5-Factor model (one global factor with four subscales) for the additional analysis in the present study. For the original ECog, the 7-Factor model was selected by the researchers in a previous analysis using a sample of

576 individuals with normal cognition, MCI and dementia (Farias et al., 2008), but those results show that the 5-Factor model also had good fit.

Baseline and Longitudinal Change in Self- and Companion-reported Everyday Function

Table 3 lists the results of the LMER model comparison for participants and companions of the five composites representing the five factors from the factor analysis. For each factor composite, three models were evaluated (null, baseline, baseline + longitudinal) separately for the participant and the companion. Smaller dAICc values and larger wAICc values indicate better fit. For participants, the model with baseline and longitudinal group effects fitted best for total ECog and visuospatial perception scores, whereas the model with a baseline group effect fitted best for memory, language, and executive function scores. For companions, the model with baseline and longitudinal group effects was best for total ECog, memory, and executive function whereas the model with the baseline group effect was best for language and visuospatial perception scores. For all companion outcomes, the same best models were selected when living together with the participant (LivingTogether) variable and its interaction with time were added to the three models for each companion outcome. In all models, the two added variables were not significant (all $ps > 0.26$), suggesting that living with the participant does not affect companion rating significantly.

Table 4 shows the results for the best models from Table 3, which were applied to the data to test for differences between each gene-expanded group and the Control group. The upper portion of Table 4 summarizes group differences for participants and companions in baseline ECog scores. For the total ECog scale and the four subscales, the baseline difference relative to controls increased going from the Low to High group. The baseline difference for the High group was positive and significant for all participant and companion scales (all $ps < 0.001$). This indicates that participants and companions in the High group reported significantly worse functioning at baseline relative to controls. The difference for the Medium group was also positive and significant for the total ECog and all subscale scores except for participant visuospatial perception, companion visuospatial perception, and companion executive function. In the Medium group, both participant and companion language scores showed the largest baseline difference compared to the other scales (estimated difference = 0.16 [p<0.001] and 0.1 [p<0.001], respectively). The difference for the Low group was not significant for any of the scales. The bottom portion of Table 4 summarizes group differences in longitudinal change for participants and companions relative to the Control group. The longitudinal differences are presented only for the total ECog scale and three subscales which showed longitudinal changes in the participant and/or companion groups (see Table 3). Participants in the Medium and High groups reported significantly greater decline longitudinally in total ECog and visuospatial perception functioning relative to controls. Companions reported significantly greater decline over time in total ECog, memory, and executive function relative to companions of the controls. The greatest longitudinal differences for the Medium and High groups were observed in companion-rated executive function scores (estimated difference = 0.062 [p = 0.026] and 0.069 [p = 0.0037], respectively). Longitudinal change in the Low group was not significant for the total ECog score or any of the subscales (all $ps > 0.2$). It was notable that unlike baseline differences, longitudinal changes in participant scores did not increase

monotonically with the gene-expansion group relative to the Control group. Rather, longitudinal change in total ECog and visuospatial-perception scores of participants in the Medium group differed more from the controls than longitudinal change in the High group. In contrast, companion measures exhibited a monotonic change with gene-expansion group except for companion memory, where longitudinal changes were similar in the Medium and High groups.

Comparisons Between Participant and Companion Ratings

A multi-response LMER analysis was conducted to ascertain whether longitudinal changes in ECog scores of participants and companions differed (see Appendix A for details of analysis). Figure 1 shows the fitted curves for each subscale using model-averaged coefficients across all possible models. All models were adjusted for the age at entry, gender, and years of education. For total ECog score, the participant (dashed line) and companion (solid line) curves in the Control, Low, and Medium groups were relatively parallel, exhibiting similar longitudinal profiles. In contrast, the High group companions reported greater functional decline over time for participants than the participants self-reported. Similarly, for memory and executive function, longitudinal changes in participant and companion curves differed only in the High group. That is, companions observed more memory and executive function decline over time than the participants in the High group reported experiencing. The discrepancy in the High group was much more important than the other groups for all three measures, which showed the slope discrepancy in the High group–total ECog, memory, and executive function (Table A.2, High group wAICc = 0.72, 0.7, and 0.91, respectively). In contrast, participants and companions reported similar longitudinal profiles of participant language and visuospatial perception function.

ECog and TFC Comparison

Companion ratings were more sensitive than participant ratings for detecting longitudinal group change for total ECog scores. Therefore, we informally compared baseline and longitudinal differences between the companion total ECog score to the TFC to assess the relative sensitivity of the ECog. At baseline, 90% of participants had the minimum possible TFC loss, indicated by a score of 3 on each TFC item leading to a loss score of zero (no loss), and 18% of the companions reported the minimum possible ECog. For those participants with repeated measures, only 18% had a change in TFC loss score over time. In contrast, 88% had a total ECog rating that changed over time.

Table 5 shows the baseline and longitudinal differences between the controls and each of the gene-expanded groups on the companion total ECog and the TFC. At baseline, the companion total ECog had a greater difference than TFC for the High group (t = 5.86 vs. 4.08), whereas the TFC had a greater difference than companion total ECog for the Medium group (t = 2.02 vs. 2.59). There was no significant baseline difference for the Low group on either measure. For the longitudinal differences, the companion total ECog had a greater difference for the Medium group (t = 2.39 vs. 1.07), whereas TFC had a greater difference for the High group (t = 3.97 vs. 2.94). There were no significant group differences in longitudinal change for the Low group for either measure. Figure 2 shows fitted curves for the companion total ECog and TFC loss by group. At baseline, the companion total ECog

had a greater difference relative to controls for the High group than TFC loss. For the Medium group, the two measures had similar baseline differences relative to controls. For longitudinal change, the longitudinal difference for the Medium group was greater for companion total ECog, whereas the difference for the High group was greater for TFC loss.

Discussion

All Everyday Cognitive Domains are Deficient in Prodromal HD

Previous work demonstrates there are mild cognitive changes in prodromal HD on sensitive and standardized neuropsychological tests (Duff et al., 2010; Harrington et al., 2012; Hart et al., 2014; Lemiere et al., 2004; Paulsen et al., 2013; Rupp et al., 2012; Stout et al., 2011). The present findings extend this work to show that changes in everyday cognition are also increasingly more evident as individuals approach a motor diagnosis. Our findings indicate that participants and companions in the Medium and High groups reported significantly worse functioning than controls in nearly all domains of everyday cognition. In the Medium group, there was significant difference relative to controls for all scales except for participant visuospatial perception, companion visuospatial perception, and companion executive function. In the High group, there was significant difference relative to controls for all scales.

Farias et al. found that everyday cognition as measured by the ECog is associated with both objective measures of neuropsychological function and measures of brain structure in a mixed group of older adults with and without cognitive impairment (2013). The relationship between everyday cognition and objective measures of cognitive functioning, as assessed on standardized neuropsychological tests of memory, language, visuospatial perception and executive function domains, and participant/companion ratings, is largely unknown in prodromal HD and needs to be investigated further. Although it has been studied to some degree in those diagnosed with HD; for example, measures of attention, processing speed and initiation have also been linked with functional difficulties in those with manifest HD (Peavy et al., 2010; Dorsey et al., 2013).When compared with controls, cross-sectional differences in cognitive performance on standardized tests are documented in individuals with prodromal HD in groups with nearer proximity to time of diagnosis (Paulsen, 2011; Stout et al., 2011). For example, measures of executive functioning, including speed/inhibition, verbal working memory, verbal learning and memory, motor planning, sensory-perceptual processing, and attention and information integration are all sensitive to worsening of cognitive function in people with prodromal HD in the Medium and High CAP groups (Harrington et al., 2012). Impaired elements of executive function have been reported in prodromal HD on a wide variety of cognitive tasks (Duff et al., 2010; Papp et al., 2013). Furthermore, baseline ratings by companions of participants' everyday executive function in the Medium and High groups are consistent with findings reported by Paulsen et al. (2013) who examined longitudinal change in the CAP groups, and by Peavy et al. (2010), who noted attention measures are among those which better define the onset of functional decline in HD. Results are also consistent with Duff et al. (Duff et al., 2010), who reported executive dysfunction impairments in ratings by companions, and Harrington et al. (2012) who documented losses in motor planning. Our findings extend these reports to the

identification of the impact of cognitive changes in daily life and familiar settings. Future studies that correlate functioning on neuropsychological tests with the ECog are needed to establish the construct validity of the subscales in prodromal HD.

Everyday Cognitive Function Decline Progresses Over Time

Everyday cognitive functioning as reported by participants and companions in the Medium and High CAP groups showed significant overall decline relative to controls over the period of study (3 years). An earlier study of people with HD (Marder et al., 2000) linked the extent of cognitive decline to the rate of functional impairment after motor diagnosis. Cognitive status was documented at baseline using standardized measures and functional decline was assessed using the TFC and the UHDRS Independence Scale (IS), both of which are examiner-administered measures. To our knowledge, ours is the first report of everyday cognitive functioning changes over time in prodromal HD groups who were stratified by proximity to diagnosis. For the participants in the Medium, defined as 7.6–12.8 estimated years until motor diagnosis, and High groups, defined as and < 7.6 estimated years until motor diagnosis (Zhang et al., 2011), total ECog function and visuospatial perception domain function declined over time relative to controls. Though companions reported significantly worse total ECog in affected individuals over time, they also reported longitudinal changes in memory and executive function. Thus, companion reports may be more sensitive to changes in everyday cognitive tasks involving memory and executive function than participant reports. This is possibly due to a diminished awareness of functional capacity, as individuals approach a manifest diagnosis. The relationship between self-report of differences in everyday cognitive function domains, formal assessments of cognition using standardized tests and measures of self-awareness will be an important avenue for future research in this area.

Everyday Cognitive Function is Reported as Early as 12 Years Before Motor Diagnosis

To our knowledge, this is the first analysis of cognition-related daily functioning activities in prodromal HD, as represented by the ECog. After finding support for a 5-factor model with baseline data, the longitudinal analysis revealed statistically significant differences between gene-expanded progression groups and gene mutation-negative controls. Longitudinal analysis also showed increasing divergence of participant and companion trajectories as progression worsened.

This study identified worsening of everyday cognitive function as reported by both participants and their companions prior to motor diagnosis of HD. This provides evidence for clinicians that decline in everyday cognitive function might be recognized by those in the prodromal stage of HD and by their companion (e.g., family members) who see them on a frequent basis. Specifically, our results indicate that changes in everyday cognitive skills are first apparent to people with prodromal HD and their companions in the Medium group, and become increasingly apparent in the High group, which is nearest to a motor diagnosis.

Companions May Provide Everyday Function Decline Data

Our finding, that participants reported slower rates of functional decline than their companions for total ECog function and for memory and executive function suggests that

proxy measures may be more reliable than self-report in detecting day-to-day functional changes in later stages of prodromal HD disease progression. This finding is consistent with our recent report from the same sample on disability in prodromal HD. We found companions reported worse decline in daily functioning and disability, as measured by the World Health Organization Disability Assessment Schedule (WHODAS) (Downing et al., 2013). It is also consistent with reports by others who documented diminished self-awareness in prodromal HD and in diagnosed HD (Duff et al., 2010; Ho et al., 2006; Hoth et al., 2007; McCusker et al., 2013). The use of proxy ratings of observable functional behavior may be most valuable for the prodomal HD population closest to motor diagnosis. The PREDICT-HD cohort is a selected group that may be more likely to notice changes. The divergence from the companion ratings found in this study may mean that companion reports could be even more significant in the general clinic population. However, proxy ratings have limitations, as they can be inadequate for evaluating internal experiences (e.g. pain, anxiety) in popluations with cognitive impairment, which can be difficult for proxies to discern (Bradford et al., 2013; Lukas, Niederecker, Gunther, Mayer, & Nikolaus, 2013).

ECog is More Sensitive than the TFC to Longitudinal Change in Specific Everyday Cognitive Abilities

We informally compared the ability of the TFC and the companion ECog to detect functional changes in prodromal HD. There are some important differences between the TFC and ECog. The ECog measures participant and companion ratings of specific cognitive function domains, while the TFC is a clinician rating of responsibilities in daily activities. The ECog showed more functional loss over time in the Medium group than the TFC. Although the ECog was able to detect functional loss in the High group, the TFC effect size was greater. The larger High group effect size for TFC is perhaps tempered by the fact that change was driven by only a minority of participants. A potentially desirable quality of the ECog is that it detected greater variability of change over time across all prodromal groups than the TFC. A majority of companion ECog ratings (88%) showed longitudinal change, whereas only a minority of TFC ratings (18%) showed longitudinal change. Baseline variability was also greater in the ECog (18% with best possible score, versus 90% for the TFC). Altogether, our results indicate that each scale provides complimentary information; both scales may be valuable in clinical trials owing to differences in the constructs assessed and their differential sensitivity to change.

Comparison of everyday cognitive function from the ECog with measures of functioning in other domains and with imaging measures of brain functioning may provide additional insights into the neurocognitive mechanisms of changes in daily functional abilities during the prodromal period. In prodromal HD, cognitive proficiency in different domains correlates with distinct patterns of cortical thinning and subcortical volume loss (Harrington et al., 2014), yet to date, the relationship between neuroimaging measures and everyday cognitive functioning has not been studied in prodromal HD. In early HD, imaging, motor and cognitive measures predict decline in total functional capacity (Tabrizi et al., 2013). Our study suggests that functional capacity is sensitive to change in prodromal HD and that the ECog may be a better instrument than the TFC for assessing functional capacity earlier in the prodromal period.

Limitations of this study include the potential for selection bias, because not all who are in the prodromal HD period participate in research. Those who participate in research may be hypervigilant, and be more likely to notice functional changes. Furthermore, knowledge of gene status may bias functional ratings and may inflate endorsement of difficulties. However, this is less likely to influence longitudinal ratings as the same bias, if present, would be operating at each assessment point. Our sample might not be representative of people with prodromal HD because most people at risk for HD do not undergo predictive genetic testing (Morrison, Harding-Lester, & Bradley, 2011; Tassicker et al., 2009). In one older study, people who chose HD genetic testing self-reported fewer anticipated problems coping with results than people who choose not to test (Codori, Hanson, & Brandt, 1994). However, we do not know if poor psychological coping translates into greater or lesser awareness or self-report of everyday functional difficulties. Furthermore, contributions of psychiatric symptoms, such as clinically-significant depression in each CAP group in the PREDICT-HD sample, (Epping et al., 2013) should be further investigated.

In this study, the length of data collection did not allow for observation of change beyond a maximum of 3.11 years. It will be necessary to confirm our findings with data from a longer follow-up period since the model with baseline group effects (Model 2) and the model with baseline and longitudinal group effects (Model 3) were relatively comparable in some cases, unlike the null model, which was virtually not supported by our data at all. No comparison was conducted with other measures of cognitive function, such as the UCSD Performance-Based Skills Assessment.

Informant report of everyday function can be subject to a number of biases that can lead to both under- and over-reporting of functional impairment (Demers, Oremus, Perrault, Champoux, & Wolfson, 2000; Ready, Ott, & Grace, 2004). For example, depression or elevated caregiver burden can lead to overestimates (Jorm et al., 1994) whereas lack of contact can lead to underestimates of functional impairment. Informant report has, however, been shown to reliably differentiate individuals with and without cognitive impairment (Farias et al., 2011; DeBettignies, Mahurin, & Pirozzolo, 1990; Isella et al., 2006; Jorm & Korten, 1988; Kemp, Brodaty, Pond, & Luscombe, 2002; Seltzer, Vasterling, Mathias, & Brennan, 2001), it is sensitive to longitudinal change (Farias et al., 2013), and it has been shown useful in predicting risk of disease progression in other populations (Farias, 2011; 2010; Daly et al., 2000; Harwood, Hope, & Jacoby, 1997; Jorm, Christensen, Jacomb, Korten, & Mackinnon, 2001). Performance-based measures of everyday function, where an individual is observed and rated on their ability to carry out functional tasks using standardized protocols (e.g., make change, write out a check), are not subject to the same biases as informant report. However, performance-based measures of everyday function come with their own set of limitations. Observed behavior during simulated tasks may differ greatly from what the individual does spontaneously in the environment. Additionally, performance-based scales are subject to practice effects and are often impractical to administer in large cohort studies due to time constraints.

In summary, we provide evidence of changes in everyday cognitive-based functional abilities for those relatively early in the course of HD. Functional changes during the prodromal HD period may well reflect subtle changes in every day cognitive functioning

that predate a motor diagnosis of HD. The ECog is sensitive to specific domains of cognitive daily functional change before motor diagnosis. Our findings suggest that companion ratings should be obtained for individuals who are closer to a manifest diagnosis because diminishing self-awareness may limit the utility of self-reported day-to-day cognitive functioning in participants approaching the onset of a motor diagnosis. The ECog may be a useful measure in clinical assessments and in future clinical trials in which these components of day-to-day function are monitored in the prodromal phase of HD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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Figure 1.
Fitted linear mixed effects regression (LMER) curves by group for participant (P) and
companion (C) Everyday Cognition (ECog) ratings.

Cont = control; Med = medium. All model coefficients were estimated adjusting for gender,
age at baseline, and years of education. The plots show the ECog subscale score as a
function of duration, person (participant or companion), and group.

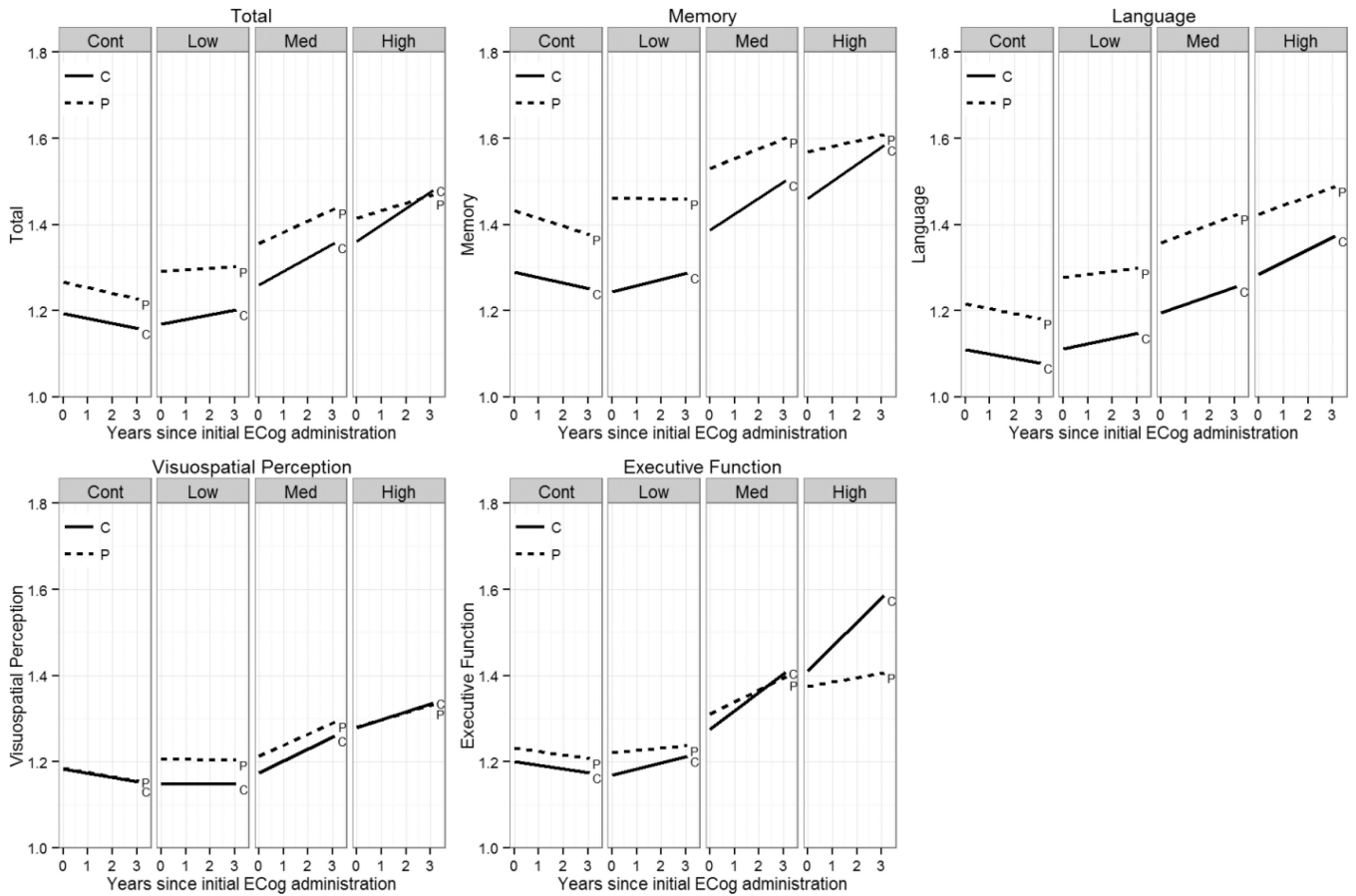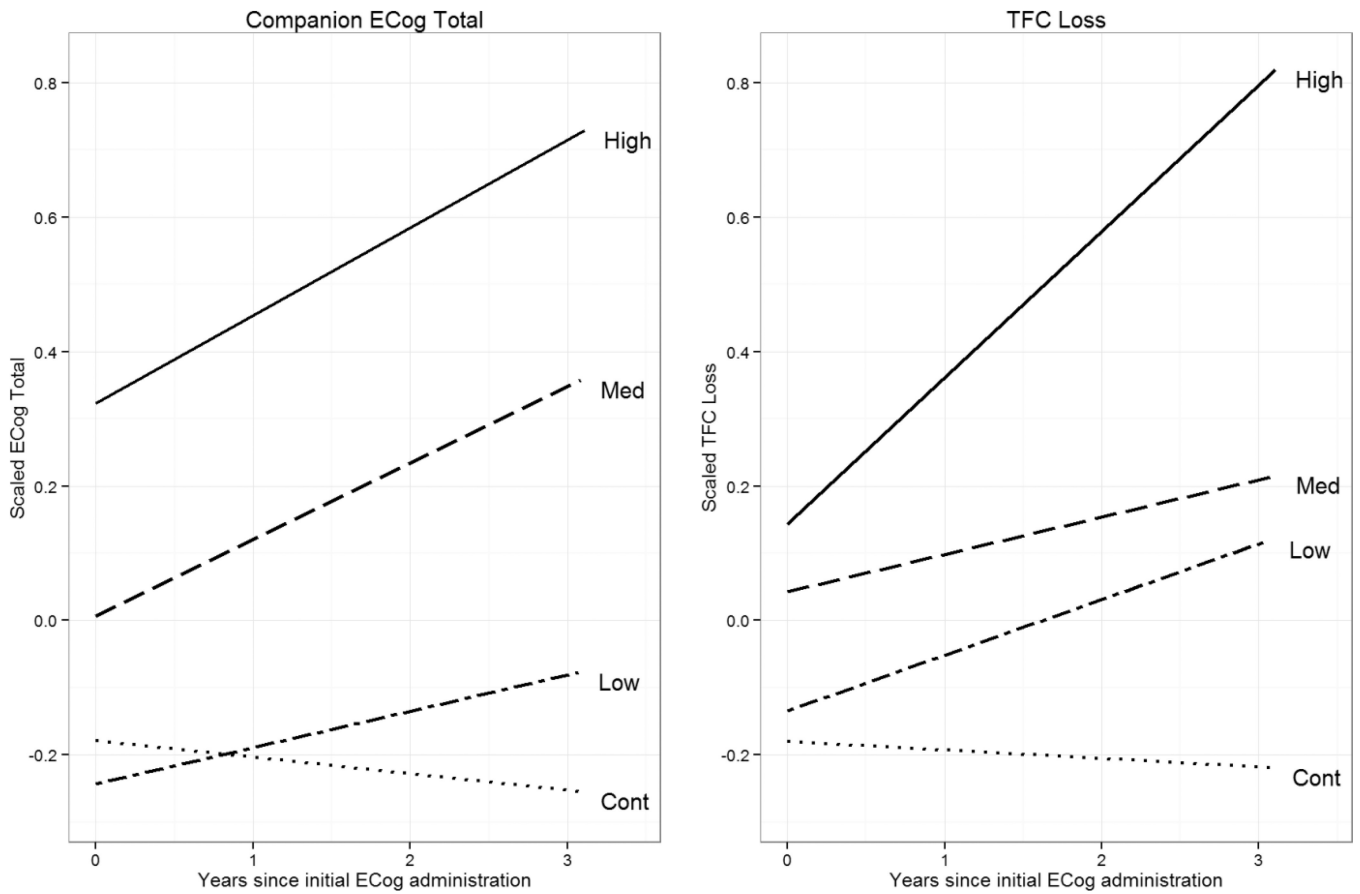**Figure 2.**
Fitted linear mixed effects regression (LMER) curves by group for scaled companion Everyday Cognition (ECog) and Total Functional Capacity (TFC) loss scores.

Cont = control; Med = medium.

All model coefficients were estimated adjusting for gender, age at baseline, and years of education. The plots show the scaled companion ECog and TFC loss scores as a function of duration and group.

Table 1

Participant Characteristics at Initial ECog Administration

Variable		Group				Group Comparison Effect Size
		Control	Low	Medium	High	
N of participants		242	158	196	254	
N of companions		223	141	178	226	
Sex (% male)		37.6	31.6	40.8	40.9	$\varphi_c = 0.07$
Age (years)	Mean	47.65	34.67	42.04	47.52	$\eta^2 = 0.18$ [a]
	SD	11.98	9.60	10.31	10.45	
CAG repeat	Mean	20.54	40.99	42.06	43.28	$\eta^2 = 0.92$ [a]
	SD	3.61	1.97	2.15	3.01	
Education (years)	Mean	15.01	14.84	14.83	14.40	$\eta^2 = 0.01$
	SD	2.48	2.43	2.44	2.77	
Participant total ECog	Mean	1.25	1.27	1.34	1.41	$\eta^2 = 0.03$ [a]
	SD	0.25	0.30	0.37	0.45	
Companion total ECog	Mean	1.19	1.15	1.23	1.37	$\eta^2 = 0.07$ [a]
	SD	0.24	0.22	0.30	0.40	
Loss of TFC	Mean	0.08	0.10	0.27	0.39	$\eta^2 = 0.03$ [a]
	SD	0.49	0.45	0.95	0.99	

Note. CAG = cytosine, adenine and guanine; ECog = Everyday Cognition scales; TFC = Total Functional Capacity scale.

[a] $p < 0.001$

Table 2

Fit Indices for Different Confirmatory Factor Analysis Models

Model	CFI	TLI	RMSEA
1-Factor Model (glob)	0.931	0.927	0.079
5-Factor Model (glob, mem, lang, vsp, exec)	**0.981**	**0.978**	**0.044**
6-Factor Model (glob, mem, lang, vsp, plan, div att)	**0.981**	**0.979**	**0.043**
7-Factor Model (glob, mem, lang, vsp, plan, org, div att)	**0.980**	**0.978**	**0.044**

Note. Glob = global; mem = memory; lang = language; vsp = visuospatial perception; exec = executive functions; plan = planning; div att = divided attention; org = organization; CFI = comparative fit index; TLI = Tucker-Lewis Index; RMSEA = root mean square error of approximation.

Fit values in **bold** indicate "good" fit.

Table 3

Separate Participant and Companion Analysis Results

Variable	Model	Group Effect	AICc	dAICc	wAICc
Participant total	1	Null	315.15	25.15	0.00
	2	Baseline	290.45	0.45	0.44
	3	**Baseline + Longitudinal**	**290.00**	**0.00**	**0.56**
Participant memory	1	Null	1762.95	12.54	0.00
	2	**Baseline**	**1750.41**	**0.00**	**0.84**
	3	Baseline + Longitudinal	1753.69	3.28	0.16
Participant language	1	Null	1111.01	42.07	0.00
	2	**Baseline**	**1068.94**	**0.00**	**0.82**
	3	Baseline + Longitudinal	1071.91	2.97	0.18
Participant vsp. perception	1	Null	218.20	11.00	0.00
	2	Baseline	208.58	1.37	0.33
	3	**Baseline + Longitudinal**	**207.20**	**0.00**	**0.66**
Participant exe. function	1	Null	955.42	19.38	0.00
	2	**Baseline**	**936.04**	**0.00**	**0.87**
	3	Baseline + Longitudinal	939.82	3.78	0.13
Companion total	1	Null	304.96	51.53	0.00
	2	Baseline	255.19	1.76	0.29
	3	**Baseline + Longitudinal**	**253.43**	**0.00**	**0.71**
Companion memory	1	Null	1186.47	34.75	0.00
	2	Baseline	1153.23	1.51	0.32
	3	**Baseline + Longitudinal**	**1151.72**	**0.00**	**0.68**
Companion language	1	Null	467.38	53.52	0.00
	2	**Baseline**	**413.86**	**0.00**	**0.73**
	3	Baseline + Longitudinal	415.86	2.00	0.27
Companion vsp. perception	1	Null	253.40	18.52	0.00
	2	**Baseline**	**234.89**	**0.00**	**0.70**
	3	Baseline + Longitudinal	236.58	1.70	0.30
Companion exe. function	1	Null	1255.49	47.06	0.00

Variable	Model	Group Effect	AICc	dAICc	wAICc
	2	Baseline	1210.34	1.91	0.28
	3	**Baseline + Longitudinal**	**1208.43**	**0.00**	**0.72**

Note. AICc = Akaike's information criterion corrected for sample size; dAICc = difference in AICc; wAICc = AICc weight; Vsp. perception = visuospatial perception; Exe. function = executive function.

The models with smallest AICc values are the best models and are displayed in boldface type. Models with smaller dAICc and wAICc closest to 1 indicate better fit.

Table 4

Baseline and Longitudinal Prodromal HD Group Differences Relative to Controls for Participant and Companion ECog

Baseline Group Difference

Variable	Low		Medium		High	
	Estimate (SE)	t-value	Estimate (SE)	t-value	Estimate (SE)	t-value
P Total	0.015 (0.039)	0.37	0.086 (0.034)	2.48^c	0.15 (0.032)	4.66^a
P Memory	0.016 (0.052)	0.31	0.11 (0.046)	2.47^c	0.15 (0.042)	3.59^a
P Language	0.07 (0.042)	1.68	0.16 (0.037)	4.27^a	0.23 (0.034)	6.62^a
P Vsp. perception	0.016 (0.036)	0.44	0.029 (0.032)	0.91	0.097 (0.029)	3.34^a
P Exe. function	−0.014 (0.044)	−0.31	0.087 (0.039)	2.24^c	0.15 (0.036)	4.19^a
C Total	−0.022 (0.035)	−0.62	0.062 (0.031)	2.02^c	0.17 (0.029)	5.86^a
C Memory	−0.038 (0.047)	−0.82	0.089 (0.041)	2.15^c	0.17 (0.039)	4.47^a
C Language	0.015 (0.033)	0.46	0.10 (0.029)	3.53^a	0.20 (0.027)	7.35^a
C Vsp. perception	−0.025 (0.032)	−0.80	0.0042 (0.028)	0.15	0.11 (0.026)	4.23^a
C Exe. function	−0.025 (0.046)	−0.53	0.069 (0.041)	1.67	0.21 (0.038)	5.57^a

Longitudinal Group Difference

Stub head	Low		Medium		High	
	Estimate (SE)	t value	Estimate (SE)	t-value	Estimate (SE)	t-value
P Total	0.012 (0.015)	0.82	0.036 (0.013)	2.71^b	0.028 (0.012)	2.30^c
P Vsp. Perception	0.011 (0.015)	0.76	0.033 (0.013)	2.55^c	0.026 (0.012)	2.27^c
C Total	0.026 (0.021)	1.23	0.047 (0.019)	2.39^c	0.052 (0.018)	2.94^b
C Memory	0.032 (0.027)	1.20	0.054 (0.024)	2.24^c	0.052 (0.022)	2.39^c
C Exe. Function	0.032 (0.029)	1.11	0.062 (0.026)	2.38^c	0.069 (0.024)	2.91^b

Note. P = participant C = companion Vsp. = visuospatial Exe. = executive.

^{a}
$p<0.001$,

[b] $p<0.01$,

[c] $p<0.05$,

Table 5

Comparison of Scaled Companion ECog and TFC Loss Between Controls and Each Gene-expanded Group

Measure	Effect	Difference With Control			
		Groups	Estimate	SE	*t*-value
Companion ECog	Baseline	Low	−0.06	0.10	−0.62
		Med	0.19	0.09	2.02 [c]
		High	0.50	0.09	5.86 [a]
	Longitudinal	Low	0.08	0.06	1.23
		Med	0.14	0.06	2.39 [c]
		High	0.16	0.05	2.94 [b]
TFC Loss	Baseline	Low	0.05	0.10	0.47
		Med	0.22	0.09	2.59 [b]
		High	0.32	0.08	4.08 [a]
	Longitudinal	Low	0.10	0.07	1.34
		Med	0.07	0.06	1.07
		High	0.23	0.06	3.97 [a]

Note. ECog = Everyday Cognition scales; TFC = Total Functional Capacity scale; Med = medium.

[a]
$p < 0.001$,

[b]
$p < 0.01$,

[c]
$p < 0.05$,

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