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# NEUROLOGY

## **Mild cognitive impairment in prediagnosed Huntington disease**

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# Mild cognitive impairment in prediagnosed Huntington disease



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## ABSTRACT

**Background:** Cognitive decline has been reported in Huntington disease (HD), as well as in the period before diagnosis of motor symptoms (i.e., pre-HD). However, the severity, frequency, and characterization of cognitive difficulties have not been well-described. Applying similar cutoffs to those used in mild cognitive impairment (MCI) research, the current study examined the rates of subtle cognitive dysfunction (e.g., dysfunction that does not meet criteria for dementia) in pre-HD.

**Methods:** Using baseline data from 160 non-gene-expanded comparison participants, normative data were established for cognitive tests of episodic memory, processing speed, executive functioning, and visuospatial perception. Cutoff scores at 1.5 standard deviations below the mean of the comparison group were then applied to 575 gene-expanded pre-HD participants from the observational study, PREDICT-HD, who were stratified by motor signs and genetic risk for HD.

**Results:** Nearly 40% of pre-HD individuals met criteria for MCI, and individuals closer to HD diagnosis had higher rates of MCI. Nonamnestic MCI was more common than amnestic MCI. Single-domain MCI was more common than multiple-domain MCI. Within the nonamnestic single-domain subtype, impairments in processing speed were most frequent.

**Conclusions:** Consistent with the Alzheimer disease literature, MCI as a prodromal period is a valid concept in pre-HD, with nearly 40% of individuals showing this level of impairment before diagnosis. Future studies should examine the utility of MCI as a marker of cognitive decline in pre-HD. *Neurology*® 2010;75:500-507

## GLOSSARY

**AD** = Alzheimer disease; **BFRT** = Benton Facial Recognition Test; **DCL** = Diagnostic Confidence Level; **HD** = Huntington disease; **HVLT-R** = Hopkins Verbal Learning Test-Revised; **MCI** = mild cognitive impairment; **PD** = Parkinson disease; **SCWT** = Stroop Color Word Test; **SDMT** = Symbol Digit Modalities Test; **UHDRS** = Unified Huntington's Disease Rating Scale.

Mild cognitive impairment (MCI) is a transitional stage between normal cognition and dementia.<sup>1</sup> It is operationally defined by subjective cognitive complaints, objective deficits (e.g., cognitive scores falling 1.5 or more standard deviations below matched peers), and the absence of dementia and functional impairment.<sup>2,3</sup> The concept of MCI has proven valuable because these individuals progress to dementia more quickly than cognitively normal peers.<sup>4</sup> Though most commonly associated with Alzheimer disease (AD),<sup>4</sup> MCI has been applied to other neurologic conditions. For example, MCI associated with vascular disease<sup>5,6</sup> can predict worsening of the disease.<sup>7</sup> Individuals with Parkinson disease (PD) can have single or multiple domain MCI,<sup>8,9</sup> and they progress to dementia at higher rates than intact peers.<sup>10</sup>

Cognitive dysfunction is one of the triad of symptoms of manifest Huntington disease (HD), with impairments in attention, verbal fluency, psychomotor speed, executive functioning, memory, and visuospatial functioning. However, the incidence of clinically relevant cognitive impairments is unknown.<sup>11-15</sup> Moreover, cognitive changes develop gradually in HD,

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with some appearing 15 years before motor signs.<sup>16</sup> Thus, early identification of MCI is of keen interest in HD, where treatment with neuroprotective agents might delay the progression of cognitive decline. The current study examined the incidence of MCI in a large sample of individuals with the genetic expansion for HD, but who did not show sufficient motor signs for a diagnosis of HD (i.e., pre-HD). Based on studies of other neurologic conditions, it was expected that some pre-HD individuals would display cognitive patterns consistent with MCI, with single-domain being more frequent than multiple-domain MCI.

**METHODS Participants.** Study participants included 160 non-gene-expanded and 575 gene-expanded individuals from the PREDICT-HD study,<sup>17</sup> a prospective observational investigation of the earliest signs and symptoms of HD. Dates of data collection were from October 2002 to April 2009. Age- and education-corrected norms were developed using the non-gene-expanded comparison participants. These individuals were a mean of 44.9 years old (SD 8.1; range 30–59), had a mean of 14.5 years of education (SD 2.8; range 8–20), and were predominantly women (70.6%) and white (100%). Comparison participants had a parent with HD, but all had CAG repeat lengths in the unexpanded range (i.e., <30).

To characterize the incidence of MCI in pre-HD, gene-expanded participants were studied. These individuals had CAG repeat lengths in the expanded range (i.e.,  $\geq 36$ ) as verified by genetic testing conducted independently from this study. Pre-HD participants were a mean of 42.1 years old (SD 7.4; range 30–59), had a mean of 14.5 years of education (SD 2.6; range 8–20), and were predominantly women (62.3%) and white (97.9%). All gene-expanded participants were classified as pre-HD based on expert raters' assessments of motor signs and functional capacity impairments that were insufficient to merit a diagnosis of HD. Motor signs were evaluated using the total motor score of the Unified Huntington's Disease Rating Scale (UHDRS), in which 31 items (e.g., ocular pursuit, finger taps, chorea) are rated on a 4-point scale ranging from normal to severe impairment. Total motor scores in the pre-HD participants suggested minimal motor signs (mean 4.5, SD 4.7). Consistent with the methods in the PREDICT-HD study, only gene-expanded participants with less than unequivocal signs of HD were included. The Total Functional Capacity score<sup>18</sup> of the UHDRS was used to quantify a patient's ability to perform basic and instrumental activities of daily living; the score is derived from reports of the pre-HD participant and his or her companion. Scores range from 0 to 13, with higher scores indicating more intact functioning. Only gene-expanded participants with no functional impairments (i.e., Total Functional Capacity score = 13) were included in the study. Pre-HD participants were stratified in 2 ways. First, using the expert ratings based on the Total Motor Score (i.e., Diagnostic Confidence Level [DCL], item 17 of the UHDRS Motor Assessment), participants were grouped by their likelihood of having HD: normal (DCL0, n = 234), nonspecific motor abnormalities (<50% confidence, DCL1, n = 246), motor abnormalities that may be signs of HD

(50%–89%, DCL2, n = 67), or motor abnormalities that are likely signs of HD (90%–98%, DCL3, n = 25). Again, participants with unequivocal signs of HD ( $\geq 99\%$ , DCL4) were excluded from these analyses. Second, estimated years to diagnosis of HD was calculated with current age and CAG repeat length.<sup>19</sup> The estimated time to HD diagnosis allowed us to stratify across 3 risk periods: near (<9 years to estimated diagnosis, n = 148), mid (9–15 years to estimated diagnosis, n = 214), and far (>15 years to estimated diagnosis, n = 213).

**Cognitive measures.** Four cognitive domains were chosen for hypothesis testing because they have all been reported to be affected in manifest HD. Episodic memory was assessed using the Hopkins Verbal Learning Test–Revised (HVLT-R). In this test, participants are given 3 trials to learn a list of 12 related words. After a 20- to 25-minute delay, free recall for the 12 words is assessed. The raw score from the delayed recall trial (number correct) was used. Processing speed was assessed using the Symbol Digit Modalities Test (SDMT). Participants have 90 seconds to use a reference key to pair as many numeric digits with corresponding geometric figures. The number of correctly paired items was used. Executive functioning was assessed by the Stroop Color Word Test (SCWT), which contains 3 trials, each lasting 45 seconds. First, participants name as many colored ink patches (red, blue, and green) as they can. Next, participants read as many color names printed in black ink (“red,” “blue,” and “green”) as they can. Then participants are again instructed to name the color ink, but of incongruous color names (e.g., respond “red” to the word “blue” printed in red ink). In this interference trial, correct responding requires suppression of the overlearned response of reading a word. The number correct from the interference trial was used. Visuospatial perception was assessed with the Benton Facial Recognition Test (BFRT). In the BFRT, participants select photographs of faces that match a target face, but vary in orientation and illumination. The number correct, of a maximum of 27, is recorded. There are no time limits for matching faces. For all 4 cognitive scores (HVLT-R, SDMT, SCWT, BFRT), raw scores are reported and higher scores reflect better performance.

**Standard protocol approvals, registrations, and patient consents.** All procedures were approved by local institutional review boards at all PREDICT-HD sites. All study participants provided written informed consent prior to data collection.

**Procedures.** Using baseline data from the comparison group, age- and education-corrected normative data were generated for each of the 4 cognitive tests. The age groupings used were 30–39, 40–49, and 50–59. The education groupings used were 12 or fewer years and more than 12 years. Within each age and education group (e.g., 40–49 years of age with more than 12 years education), cutoff scores were determined that fell at 1.5 standard deviations below the mean, which is a common demarcation point for the identification of MCI. The cutoff scores from the comparison group were then applied to the pre-HD participants to determine the frequency of MCI in the large cohort. Amnesic MCI was defined as a memory score (i.e., HVLT-R) falling below the comparison cutoff. Nonamnesic MCI was defined as at least one nonmemory score (i.e., SDMT, SCWT, BFRT) falling below the comparison cutoff. Within the amnesic and nonamnesic categories, single-domain MCI was defined as only 1 cognitive score falling below the comparison cutoff, whereas multiple-domain MCI was defined as 2 or more cognitive scores falling below the comparison cutoffs.  $\chi^2$  was

**Table 1** Percentage of pre-HD participants falling below the 1.5 standard deviation cutoff value by subtype

Group	No MCI	Amnesic MCI		Nonamnesic MCI	
		Single	Multiple	Single	Multiple
Comparison	80.3	5.1	1.9	9.0	3.8
All pre-HD	60.2	7.5	9.3	18.4	4.6
<b>DCL</b>					
DCL0	66.2	6.8	5.6	17.1	4.3
DCL1	58.5	7.7	10.6	18.7	4.5
DCL2	52.2	10.5	14.9	19.4	3.0
DLC3	36.0	4.0	20.0	28.0	12.0
<b>Nearness to onset</b>					
Far	72.7	6.2	2.9	14.4	3.8
Mid	57.8	8.9	8.0	20.2	5.2
Near	46.0	7.4	20.3	21.6	4.7

Abbreviations: DCL = diagnostic confidence level; HD = Huntington disease; MCI = mild cognitive impairment.

used to compare groups (comparison and pre-HD) on percentage with MCI subtypes.

**RESULTS Non-gene-expanded comparison participants.** On average, raw scores on the cognitive tests in the non-gene-expanded comparison participants fell within the normal range compared to normative data from test manuals (HVLRT-R: mean 10.0, SD 2.0 [47th percentile]; SDMT: mean 53.7, SD 8.8 [55th percentile]; SCWT Interference: mean 46.2, SD 8.8 [55th percentile]; BFRT: mean 23.0, SD 1.9 [71st percentile]). For our entire comparison group, cutoff scores at 1.5 standard deviations below the mean were HVLRT-R 7.1, SDMT 40.4, SCWT Interfer-

ence 33.0, and BFRT 20.2. Note that these cutoffs are based on the entire sample (i.e., collapsed across age and education groupings), and the individual group cutoff scores can be obtained from the first author.

**Gene-expanded pre-HD participants.** Table 1 summarizes the percentage of pre-HD participants who scored 1.5 or more SDs below our comparison group cutoff for each MCI subtype. When each pre-HD participant was compared to his or her age- and education-corrected cutoff score, 39.8% of the gene-expanded pre-HD participants were identified as having some type of MCI (i.e., at least one cognitive domain falling 1.5 or more standard deviations below the comparison group). The majority of these individuals were classified as having a nonamnesic MCI subtype (18.4%), with fewer having an amnesic subtype (7.5%). Within both amnesic and nonamnesic subtypes, single-domain MCI was much more common than multiple-domain MCI (26.0% vs 13.9%). Within all pre-HD participants, deficits in processing speed were the most common followed by episodic memory and visuospatial processing impairments (table 2). MCI in executive functioning was least common.

Those pre-HD participants who presented with more motor abnormalities (and greater expert rater confidence of emerging HD) had higher rates of MCI (DCL0 = 33.8%, DCL1 = 41.5%, DCL2 = 47.8%, DCL3 = 64.0%,  $p < 0.0001$  for trend). Additional details about the MCI subtypes and cognitive domains affected as they relate to motor abnormalities are presented in tables 1 and 2.

**Table 2** Percentage of pre-HD participants falling below the 1.5 standard deviation cutoff value by cognitive domain

Group	Single domain				Multiple domain								
	M	PS	EF	VSP	M + PS	M + EF	M + VSP	PS + EF	PS + VSP	EF + VSP	M + PS + EF	PS + EF + VSP	M + PS + EF + VSP
Comparison	5.1	3.2	3.2	2.5	1.3	0.6	0.0	1.9	0.6	1.3	0.0	0.0	0.0
All pre-HD	7.5	9.1	3.1	6.3	3.3	0.8	0.7	1.7	1.0	1.0	2.1	0.7	0.9
<b>DCL</b>													
DCL0	6.8	6.4	1.7	9.0	2.6	0.0	0.4	0.6	0.3	0.8	1.7	0.9	0.4
DCL1	7.7	10.6	4.1	4.1	3.7	0.4	0.8	1.6	1.6	0.8	2.9	0.4	0.8
DCL2	10.5	10.5	3.0	6.0	6.0	3.0	1.5	1.5	0.0	1.5	1.5	0.0	1.5
DLC3	4.0	16.0	8.0	4.0	0.0	8.0	0.0	4.0	0.0	4.0	4.0	4.0	4.0
<b>Nearness to onset</b>													
Far	6.2	4.8	1.9	7.7	1.4	0.5	0.0	1.0	1.0	1.0	0.5	1.0	0.5
Mid	8.9	10.8	4.7	1.4	0.7	0.3	0.9	1.9	1.4	1.4	1.9	0.5	0.0
Near	7.4	12.8	2.7	1.2	1.5	0.3	1.4	2.7	0.7	0.7	4.7	0.7	2.7

Abbreviations: DCL = diagnostic confidence level; EF = executive functioning; HD = Huntington disease; M = memory; MCI = mild cognitive impairment; PS = processing speed; VSP = visuospatial perception.

As pre-HD participants got closer to estimated diagnosis based on their genetic risk, the prevalence of MCI increased (far = 27.3%, mid = 42.3%, near = 54.1%;  $p < 0.0001$  for trend). Pre-HD participants who were near (<9 years) or midway (9–15 years) to diagnosis had higher rates of MCI than the comparison group ( $p < 0.0001$ ), while those who were far (>15 years) from diagnosis did not ( $p = 0.10$ ). Nearness to diagnosis appeared to lead to different patterns of MCI subtypes. Whereas nonamnestic MCI demonstrated a linear increase with nearness to diagnosis, the amnestic subtype was less linear. Single-domain MCI was more common in both the far and mid pre-HD participants (far: single = 20.6%, multi = 6.7%; mid: single = 29.1%, multi = 13.2%), but single and multiple-domain MCI were equally common in those near to diagnosis (single = 29.1%, multi = 25.0%). In those far from diagnosis, visuospatial perception and episodic memory were the most common single-domain subtypes (see table 2). In those mid and near diagnosis, processing speed and episodic memory were most commonly affected.

**DISCUSSION** Cognitive deficits have been widely reported in pre-HD and manifest HD,<sup>11–15</sup> but the prevalence of MCI in HD has not been previously examined. In a large cohort of individuals who were estimated to be over 14 years from a motor diagnosis of HD, we found that nearly 40% displayed mild impairments in episodic memory, processing speed, executive functioning, and/or visuospatial perception. These pre-HD individuals met existing criteria for MCI, as they did not have dementia and were not experiencing functional decline, but did show evidence of cognitive deterioration using standard criteria for MCI (i.e., decline in performance by 1.5 or more standard deviations relative to age- and education-matched normative data). The rates of MCI observed in this pre-HD cohort are notably higher than MCI rates reported in non-HD geriatric samples (e.g., 4% of amnestic MCI),<sup>20</sup> although this appears to be the first study to examine the prevalence of MCI in a young, pre-HD cohort.

Unlike distributions seen in AD, the nonamnestic MCI subtype was more than twice as frequent as the amnestic subtype in this cohort of pre-HD individuals. In some ways, this is not surprising,<sup>21</sup> as few (if any) of these individuals are expected to progress to AD, given their known risk of HD. However, consistent with MCI in other neurologic disorders, single-domain MCI was more common than multiple-domain MCI. Nearly twice as many gene-expanded participants demonstrated isolated cognitive deficits as those with multiple-domain impairments (e.g.,

single-domain MCI = 25.9%, multiple-domain MCI = 13.9%). We suspect that single-domain MCI may reflect an earlier point in the transition between normal cognition and dementia, and that multiple-domain MCI represents a later point in the progression of cognitive dysfunction.

When individual cognitive domains were examined, processing speed (9.1%) and episodic memory (7.5%) were most commonly affected in pre-HD. This finding is consistent with reports of cognitive deficits in both manifest HD and pre-HD. For example, differences between gene-expanded and non-gene-expanded participants have been observed on a range of cognitive measures, including those assessing processing speed.<sup>17</sup> Similarly, multiple studies have identified impairments in learning and memory in patients with HD.<sup>14,22</sup> Given the prevalence of deficits in these 2 cognitive domains in our study, they might serve as targets for early intervention in clinical trials. However, it should be noted that only the processing speed measure had a linear trend across all 3 phases of pre-HD (near, mid, far), which might make this the best candidate target for those clinical trials. Somewhat surprisingly, the rate of the executive dysfunction MCI subtype was the lowest of the 4 domain subtypes examined, irrespective of the estimated time to HD diagnosis. Response inhibition on the SCWT does not fully capture the multifaceted domain of executive functioning. Future studies should utilize multiple measures of executive functioning to investigate MCI in this domain.

Not only is MCI relatively common in pre-HD, but it appears associated with onset of HD. As more motor abnormalities were observed in these patients (i.e., higher DCLs), MCI rates increased. For example, 33.8% of individuals rated as motorically normal (i.e., DCL0) were classified with some type of MCI, whereas 64% of individuals with motor signs likely to be HD (i.e., DCL3) had MCI. Such findings indicate that when motor signs are observed in these patients, a referral for a neuropsychological evaluation is also likely needed. MCI risk also appears related to genetic risk of HD, as individuals approaching estimated diagnosis (based on CAG repeat length and current age) had double the rates of MCI (e.g., 27.3% and 54.1% of the far and near participants). These findings indicate that MCI represents a prodromal period in HD, similar to the transitional stage in AD and other neurodegenerative conditions.

Our findings have both clinical and research implications. For health care providers, greater attention needs to be directed toward MCI in pre-HD. Despite being “presymptomatic,” a sizable minority of this relatively young cohort is falling well below expectations in a broad range of cognitive domains.



Although statistically significant declines in cognition relative to controls have been reported in gene-expanded and non-gene-expanded individuals,<sup>16-17</sup> the clinical significance of these cognitive changes was not examined. This information is vital for development of diagnostic criteria that would better aid in the early identification of the MCI phase of the disease. The need for early identification of MCI is partly driven by the evolution of putative neuroprotective agents that ideally would be administered when pathology is first detected. Additionally, since many pre-HD individuals are working and raising families, they may actually be experiencing some mild functional difficulties in daily life that are not captured by the functional capacity scale of the UHDRS. Interventions, such as cognitive rehabilitation or cognitive-enhancing medications, might be useful in remediating the early effects of HD. From a research standpoint, our results raise the possibility that pre-HD individuals with MCI could represent a subgroup of all pre-HD individuals. Those with MCI might be closer to HD diagnosis. These more-at-risk individuals might be better candidates for disease-modifying clinical trials, especially trials that use cognition as a primary endpoint.

The present study is a first step toward characterizing clinically relevant MCI in pre-HD. Though we examined 4 cognitive domains commonly affected in HD, other cognitive domains (e.g., learning, language, construction, higher level problem-solving) clearly merit study. We also only examined baseline prevalence rates of MCI, whereas future studies should longitudinally investigate the prognostic value of MCI in pre-HD. As with AD, vascular cognitive impairment without dementia, and PD, the concept of MCI in pre-HD is much more valuable if individuals exhibit faster cognitive decline or higher rates of progression to dementia. If MCI-positive individuals convert at higher rates, this information could better inform clinical and personal decision-making by practitioners, patients, and their families. Clinical trials of pre-HD could also be more efficient if samples were enriched with cases of MCI. Likewise, neuroimaging studies of MCI-positive and MCI-negative pre-HD might advance an understanding of the neurobiology of cognitive decline in HD, just as studies of cerebral atrophy and metabolic hypoperfusion have in other etiologies of MCI. Finally, it would be useful to identify the prevalence of MCI in patients with manifest HD.

One notable limitation of the current study was its incomplete classification of MCI. In AD, MCI is typically operationally defined by 4 criteria: subjective cognitive complaint, objective cognitive deficit, absence of functional impairments, and absence of

dementia.<sup>1,2</sup> Our study provided information about 3 of the criteria, whereas data on subjective cognitive complaints were not collected. Although this leaves us unsure about how much of a concern MCI is in pre-HD, this might be the least valuable diagnostic criterion given that the presence of subjective cognitive complaints tends to be quite variable in MCI and may have less predictive utility than objective cognitive deficits.<sup>23</sup> Additionally, individuals with pre-HD and manifest HD may have decreased awareness,<sup>24,25</sup> which could render subjective cognitive complaints of limited value in this population. Nonetheless, future studies might also collect subjective information about cognitive functioning from both patients and collateral sources. Another limitation of the current study is in its samples. Individuals who participate in PREDICT-HD might not represent all pre-HD individuals, as only the minority of at-risk individuals get the genetic test for HD. However, this selection bias is largely unavoidable for this type of research. A third limitation of the study was that cognitive domains were only represented by a single neuropsychological test rather than multiple tests that assess that domain; future studies might employ a broader assessment battery. We also did not systematically exclude participants with elevated depression scores. Though increased depression has been linked with MCI in other studies,<sup>26,27</sup> and depression can occur in HD, studies of this pre-HD cohort suggest minimal depressive symptoms.<sup>17,28</sup> Nonetheless, future studies might examine the relationship between depression and MCI in pre-HD.

## AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by James Mills and Dr. Langbehn.

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**Mild cognitive impairment in prediagnosed Huntington disease**

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