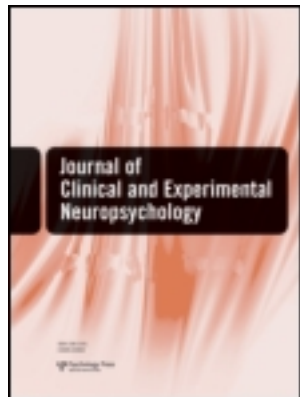


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Difficulty modifying a sustained motor response in prodromal Huntington's disease

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We investigated the nature of motor symptoms in the preclinical stage of Huntington's disease. Individuals with the CAG expanded repeat of Huntington's disease (prHD) and two control groups were tested on a task requiring a releasing movement (releasing a depressed button) followed by a ballistic movement (pressing a different button). Movement times were measured separately for releasing and ballistic movements. The mean reaction time of the prHD group was significantly longer when releasing a movement than that of the other groups. The groups, however, did not differ significantly on movement time for ballistic movements. Our results show that motor slowing is evident prior to the clinical diagnosis of Huntington's disease and may reflect difficulty in modifying a sustained motor program.

Keywords: Huntington's disease; Prodromal; Preclinical; Motor; Modify movement.

Huntington's disease (HD) is caused by expanded CAG trinucleotide repeats (The American College of Medical Genetics/American Society of Human Genetics Huntington Disease Genetic Testing Working Group, 1998) on the IT15 gene on chromosome 4 (The Huntington's Disease Collaborative Research Group, 1993). Individuals with 36 or more CAG repeats and without diagnosable motor impairments are considered "prodromal" for HD (prHD). prHD individuals receive a clinical diagnosis after a neurologic exam identifies evidence of movement symptoms associated with HD (Potter, Spector, & Prior, 2004). A number of studies have found subtle movement symptoms in carriers of the Huntington's disease gene (Blekher, T., et al., 2006; Foroud, et al., 1995; Kirkwood et al., 1999; Kirkwood et al., 2000; Paulsen et al., 2008; Rao, Gordon, & Marder, 2011; Rao, Muratori, Louis, Moskowitz, & Marder, 2008;

Rupp et al., 2010; Siemers et al., 1996; Snowden, Craufurd, Thompson, & Neary, 2002; Tabrizi et al., 2009). For example, in a longitudinal study, Rowe et al. (2010) measured timing in a large sample of prHD and found a significant difference between prHD and HD negative individuals, who have a parent with HD but do not have the expansion, on the precision of the timing but not on the speed.

Examining different components of motoric actions could yield new methods for characterizing abnormal motor symptoms that are common in a prodromal phase of HD. Smith, Brandt, and Shadmehr (2000) measured feedforward processes (predicting, planning, and executing a movement that has not been made; Seidler, Noll, & Thiers, 2004) and feedback processes (making adjustments to movements already in progress; Seidler et al., 2004) in individuals from four subject groups (including manifest and prodromal HD). The task

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required that participants reach quickly for targets while holding a manipulandum (a device that measures arm movements). Two types of errors occurred during the course of the movements that the subject had to correct: subject error or experimenter error (the manipulandum was jolted). Interestingly, prHD participants were slower compared to their respective control group to correct their internally or externally generated movements (errors), suggesting that motor dysfunction associated with HD may begin as dysfunction in error feedback control. This interpretation is consistent with the observation that the basal ganglia, which are early targets for HD neurodegeneration (Aylward et al., 2004; Harris et al., 1999; Kipps, Duggins, Mahant, Gomes, Ashburner, & McClusker, 2005), are critical for the feedback control of motor behavior (Seidler et al., 2004).

We investigated the possibility that an even more fundamental problem marks the onset of motor dysfunction associated with HD. Feedback control often incorporates a modification of a currently active motor program to allow for corrections to occur, or to initiate alternative motor programs (Seidler et al., 2004). If prHD individuals have difficulty modifying or releasing a motor program that is already engaged, then they would, as a result, also have difficulty correcting errors that are either internally or externally generated. To address this question in our current study, prHD, HD negative (with a family history of HD), and healthy comparison participants were instructed to release a button as soon as a light appeared (“release”) and then press another button (“ballistic movement”) as quickly as possible.

METHOD

Participants

Participants were grouped according to genetic status and family history of HD. Inclusion criteria for the prHD group included (a) individuals who have/had a parent diagnosed with HD, and (b) had genetic test results showing more than 36 CAG repeats (Potter et al., 2004). Exclusion criteria for prHD included a clinical diagnosis of HD based on motor symptoms rated “probable or unequivocal” signs according to the Unified Huntington’s Disease Rating Scale (UHDRS; Huntington Study Group, 1996) guidelines. Using the Langbehn method (Langbehn, Brinkman, Falush, Paulsen, & Hayden, 2004) to predict age of disease onset, the prHD group was estimated to be an average of 16.09 ($SD = 8.11$) years from onset.

The second group was the HD negative group and included participants with a parent with HD but fewer than 27 CAG repeats (Potter et al., 2004). The experimenters were blind to genetic status. The third group, the community control (CC) group, included for comparison purposes, consisted of participants who reported no family history of HD. These participants were matched to the prHD individuals on age, gender, and education. The three groups were similar on demographic variables and overall cognitive ability as measured by the Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975; Table 1). Also, a computerized version of a standard measure of attention, the Digit Span test (Wechsler, 1997), was administered. Digits were presented visually in strings at a rate of 1 digit per second. Once prompted, participants entered the digits, in the same order of presentation (commonly known as Forward Digit Span) and in the reverse order of presentation (commonly known as the Backward Digit Span), as quickly and accurately as possible. The number of forward and backward digits strings recalled were summed for each participant and then averaged, and response times for forward and backward were averaged. There were no significant group differences (Table 1).

Written informed consent was obtained from all participants after the study procedures were fully explained. The procedures were approved by the Human Research Protections Program at the University of California, San Diego (UCSD). The prHD and HD negative participants were recruited from the UCSD Huntington’s Disease Clinical Research Center (HDCRC). Although initial symptoms can be nonmotoric, the senior neurologist based her diagnosis on the emergence of motor symptoms, following standard procedures of the motor portion of the UHDRS (Huntington Study Group, 1996). Exclusion criteria were positive history of alcoholism, drug abuse, learning disability, and severe neurologic or psychiatric illness. The CC participants were recruited from ongoing studies at the UCSD HDCRC and through the UCSD Psychology department participant pool. Participants in the CC group were not tested for the CAG repeat expansion associated with HD, but none had any indication of a family history of HD.

Task

Participants sat squarely in front of a laptop and were instructed to use the index finger of their dominant hand to depress the space bar. Participants maintained this response until a light flashed briefly on the screen (for 250 ms). They then released the

TABLE 1
Mean of demographic and cognitive variables for three subject groups

<i>Status</i>	<i>n</i>	<i>Age (years)</i>	<i>Education (years)</i>	<i>Sex (% female)</i>	<i>CAG repeat number</i>	<i>MMSE</i>	<i>Digit Span response time (ms)</i>	<i>Digit Span total</i>
prHD	26	41 (12)	16 (2)	46	41.76 (1.64)	28.14 (2.85)	5,217 (1,496)	8.25 (2.59)
HD negative	16	43 (12)	15 (2)	67	21.38 (4.23)	27.71 (1.77)	5,533 (1,026)	7.46 (1.90)
CC	26	41 (12)	16 (1)	46		29.17 (1.15)	4,801 (1,419)	8.67 (3.18)

Note. prHD = prodromal positive for HD CAG expansion; HD negative = prodromal negative for HD CAG expansion; CC = community control participants; MMSE = Mini Mental State Examination. Standard deviations in parentheses.

space bar and pressed the “y” key as quickly as possible for 14 trials (and 6 practice trials). The time between light onset and spacebar release was a measure of release movement. The time between spacebar release and y-key press was a measure of ballistic movement.

Analysis

First, for descriptive purposes, we performed an analysis of variance (ANOVA) on the untransformed dependent measures. Next, to make the comparison between the two types of responses (release and ballistic movements) more meaningful, we transformed scores from the prHD and HD negative to z scores relative to CC performance. Using this approach, any difference between the performance of a participant with a family history of HD and the mean performance of the CC participants (e.g., for release movements) is scaled with respect to the CC standard deviation. This transformation is useful because a small absolute impairment on a task with low variability might reflect a greater impairment than a larger absolute difference on a task with greater variability (the opposite of what would be concluded by focusing on the absolute differences). Converting to z scores addresses this issue by expressing performance in terms of standard deviation units. Individual prHD and HD negative z scores were computed using the formula: $z_i = (x_i - \mu) / \sigma$, where z_i is the z score for a prHD or HD negative individual, x_i is the prHD and HD negative score (e.g., the raw release movement score), μ is the group mean score from CC, and σ is the standard deviation of the CC scores. We also computed a second z score transformation of the prHD scores based on the mean and standard deviation of the HD negative and CC groups combined.

Receiver operating characteristic (ROC) analysis is a standard method for quantifying the diagnostic information associated with a continuous measure (Metz, 1978). In our case, the continuous measure consisted of release times, and it was used to compute the true positive rate (i.e., the proportion of the prHD that were correctly identified) and the false positive rate (i.e., the proportion of the comparison group incorrectly identified) associated with various release-time cutoffs. For example, we first used a cutoff of 300 ms, where the true positive rate consists of the proportion of prHD individuals whose release times exceeded 300 ms, and the false positive rate consists of the proportion of controls whose release times exceeded 300 ms. This pair of values yielded one point on the ROC. Next, we used a cutoff of 250 ms, where the true positive rate now equals the proportion of prHD individuals whose release times exceeded 250 ms, and the false positive rate consists of the proportion of controls whose release times exceeded 250 ms. This pair of values yielded a second point on the ROC. This process of reducing the cutoff in 50-ms increments was continued until it reached a cutoff of 50 ms (which yielded a total of 7 points on the ROC). The further the ROC points bow away from the diagonal, the better able the release-time measure is to distinguish between the two groups.

RESULTS

Two prHD, three HD negative, and two CC participants were outliers (their release and ballistic movement scores were beyond the Tukey outer fence; Tukey, 1977) and were removed from the analyses. Analyses were conducted on the remaining 26 prHD, 15 HD negative and 26 CC participants.

A one-way ANOVA was conducted on release and ballistic movements with group status as the between-subjects factor. The mean reaction time

for release movements was significantly longer for the prHD group ($M = 211.23$, $SD = 62.84$) than for the HD negative and CC groups ($M = 162.87$, $SD = 35.00$; and $M = 150.04$, $SD = 55.44$, respectively), $F(2, 64) = 8.69$, $p < .001$. The mean time for ballistic movements was also longer for the prHD group ($M = 333.69$, $SD = 115.95$) than for the HD negative and CC groups ($M = 304.13$, $SD = 67.26$; and $M = 283.96$, $SD = 107.10$, respectively), but this effect was not significant, $F(2, 64) = 1.51$, $p = .228$.

To evaluate whether the degree of impairment for release movements differed from the degree of impairment for ballistic movements, we converted prHD and HD negative movement times to z scores using the mean and standard deviation of the movement times provided by the CC group. A positive z score indicated a longer movement time than the average CC movement time. Figure 1A shows the z scores of the prHD and HD negative groups. An ANOVA revealed a significant difference between these two groups in movements, $F(1, 39) = 4.62$, $MSE = 6.29$, $p = .038$, and movement type, $F(1, 39) = 4.46$, $MSE = 2.23$, $p = .041$. The interaction between movement type and disease status was a nonsignificant trend, $F(1, 39) = 3.36$, $MSE = 1.68$, $p = .075$.

Because the movement times for the HD negative and CC groups did not differ significantly for either release or ballistic movements, we combined these two groups to increase statistical power and standardized the prHD scores relative to the combined control group. As shown in Figure 1B, the prHD group was more severely impaired on releasing a movement than on the ballistic movement, $t(25) = 2.91$, $p = .007$. Thus, the data indicate that releasing an already engaged motor program is differentially affected in individuals who are in the prodromal stage of the disease.

ROC analysis of the release time data can be used to classify participants into the prHD and combined control groups with reasonable precision. For example, for average release times of 201–250 ms, the true positive rate is .54 and the false positive rate is .15 (Figure 1C).

DISCUSSION

There is little research on midflight correction and release movements in prHD individuals. The goal of the current experiment was to test individuals in the preclinical stage of HD on feedforward and feedback controlled movements. Prior research indicates that patients with HD are slowed on

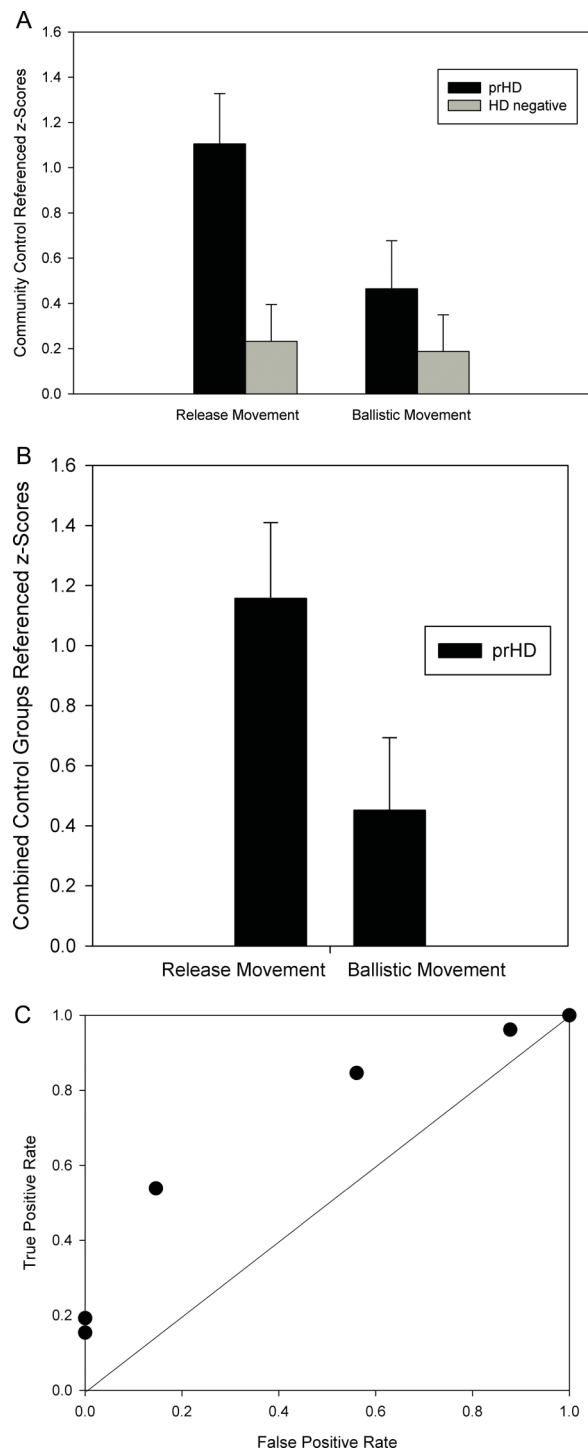


Figure 1. (A) Community control (CC) group referenced z score averages for release and ballistic movements for the prHD (prodromal positive for HD CAG expansion) and HD negative (prodromal negative for HD CAG expansion) groups. (B) Control groups combined referenced z score averages for release and ballistic movements for the prHD group. (C) Receiver operating characteristic (ROC) for release time data illustrating true positive rate (prHD individuals correctly classified as prHD) and false positive rate (HD negative/CC misclassified as prHD) for release times cutoff in 50-ms increments.

both phases of a similar task (van Vugt et al., 2004). By contrast, our results show that prHD participants exhibit differential slowing on the first (release) phase of the task compared to HD negative and CC participants. While this result could be interpreted as a selective deficit in response initiation, an important consideration is that the task begins with an active motor program already in place (i.e., as participants are pressing the space bar, they are predicting and planning the release of the spacebar and movement to the “y” key). Thus, our results may point to a more specific deficit in the ability to release or modify a preloaded motor program in prHD participants (i.e., feedback motor response is affected). These findings could also be interpreted in terms of a task-switching deficit, which has been previously documented in HD (Aron et al., 2003). Here, the deficit would involve switching from a preloaded motor program (depressing a button) to a new motor program (making a ballistic movement).

We used a measure of attention, digit span, to rule out the possibility that impaired disengagement of attention could explain the results. Consistent with findings reported by Lemiere, Decruyenaere, Evers-Kiebooms, Vandebussche, and Dom (2002), the prHD group performance on digit span was no different from that of the comparison groups. It is, therefore, reasonable to conclude that attention deficits are not driving the motor differences we observed.

Our results, showing that there is slowing when releasing or modifying a motor program, are consistent with the small body of literature on timing in prodromal HD and in error feedback in prodromal HD. Difficulties with releasing a movement would be reflected in the precision of timing (Rowe et al., 2010). Also, our findings are compatible with those of Smith et al. (2000), though we conceptualize them in a different way. They reported that prHD individuals have difficulty executing a “midflight” correction. Whereas they interpreted that result to reflect feedback control errors, it is conceivable that it instead reflects a more fundamental difficulty in releasing an engaged motor program. If one has difficulty releasing an engaged motor program, midflight correction might be impaired for that reason alone. Although our findings raise this possibility, further investigations will be needed to substantiate it.

In addition to making a theoretical contribution, the task described in this paper may have clinical utility as well. To that end, future efforts will measure test–retest correlations, associations between task variables and other disease markers (e.g., UHDRS clinical measures,

diffusion tensor imaging markers, disease burden indicators), longitudinal changes (i.e., with performance measured at several time points during the asymptomatic stage), and corresponding imaging data. The procedure could serve as a sensitive behavioral marker in individuals at risk for HD prior to the onset of prominent motor symptoms. The task takes less than five minutes to administer and does not require complex analyses to interpret the results. The benefits of such a marker could be widespread as its utility may generalize to and advance understanding of other diseases affecting the basal ganglia, such as Parkinson's disease, multiple sclerosis, and HIV-associated dementia.

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