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Progression in prediagnostic Huntington disease

Jason Rupp¹, Tanya Blekher², Jacqueline Jackson¹, Xabier Beristain³, Jeanine Marshall¹, Siu Hui⁴, Joanne Wojcieszek³, and Tatiana Foroud¹

¹Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana, USA

²Department of Ophthalmology, Indiana University School of Medicine, Indianapolis, Indiana, USA

³Department of Neurology, Indiana University School of Medicine, Indianapolis, Indiana, USA

⁴Department of Medicine, Division of Biostatistics, Indiana University School of Medicine, Regenstrief Institute, Indianapolis, Indiana, USA

Abstract

Objective—To examine rates of decline in individuals at risk for Huntington disease (HD).

Methods—106 individuals at risk for HD completed a battery of neurocognitive, psychomotor and oculomotor tasks at two visits, approximately 2.5 years apart. Participants were classified as: (1) without the CAG expansion (normal controls, NC; n=68) or (2) with the CAG expansion (CAG+; n=38). The CAG+ group was further subdivided into those near to (near; n=19) or far from (far; n=19) their estimated age of onset. Longitudinal performance in the CAG+ group was evaluated with a repeated measures model with two main effects (time to onset, visit) and their interaction. Analysis of covariance was employed to detect differences in longitudinal performance in the three groups (NC, near and far).

Results—In the CAG+, the interaction term was significant ($p \leq 0.02$) for four measures (movement time, alternate button tapping, variability of latency for a memory guided task and percentage of errors for a more complex memory guided task), suggesting the rate of decline was more rapid as subjects approached onset. Longitudinal progression in the three groups differed for several variables ($p < 0.05$). In most, the near group had significantly faster progression than NC; however, comparisons of the NC and far groups were less consistent.

Conclusions—Different patterns of progression were observed during the prediagnostic period. For some measures, CAG+ subjects closer to estimated onset showed a more rapid decline while for other measures the CAG+ group had a constant rate of decline throughout the prediagnostic period that was more rapid than in NC.

INTRODUCTION

Huntington disease (HD) is an autosomal dominant disorder characterised by progressive decline of motor, cognitive and behavioural function. The disease causing mutation is a trinucleotide (CAG) repeat expansion in the 5' translated region of the huntingtin gene.¹ The

Correspondences to Dr T Foroud, Indiana University School of Medicine, 410 W 10th Street (HS 4021), Indianapolis, IN 46202-5251, USA; tforoud@iupui.edu.

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average age of onset is 40 years although onset occurs as early as age 2 and as late as age 80.²³

Disease onset is insidious, often with a long prediagnostic period prior to the clinical diagnosis. Typically, diagnosis is made based on the presence of unequivocal motor signs consistent with HD. Unfortunately, there are no current pharmacological or therapeutic interventions shown to delay or slow the onset or progression of HD. Therefore, it is essential that sensitive and specific biomarkers in the prediagnostic period be identified that could be used to evaluate future therapeutic interventions.

Several studies have sought to identify potential prediagnostic biomarkers. Some cross sectional studies reported that prediagnostic CAG expanded individuals (CAG+) exhibited deficits in tests of attention,⁴ executive function,⁵ memory,^{4,5,7-9} psychomotor speed^{4,8} and ocular movements¹⁰⁻¹⁴; however, other studies of these same domains have not confirmed these results.¹⁵⁻²¹ In a large cross sectional sample of 438 prediagnostic individuals, Paulsen and colleagues²² reported that the commencement of detectable changes begins one to two decades prior to the estimated age of onset, and this initial period is followed by more rapid change in the years just prior to diagnosis. Few studies have explored longitudinal rates of decline in prediagnostic CAG+ individuals. There have been reports of differential rates of progression between prediagnostic CAG+ and non-expanded (CAG-) controls in measures of attention, psychomotor speed and memory²³⁻²⁷; however, others have not been able to replicate these results.^{18,28-30} These discrepant results may be due to the modest sample sizes of most studies.

The goal of this study was to examine longitudinal rates of change in a sample of at risk individuals for a series of neurocognitive, psychomotor and oculomotor measures. We use estimated time to onset in two ways: (1) as a continuous variable to evaluate change within a group of CAG+ individuals and (2) as a means of dichotomising a group of CAG+ individuals (into those 'near' and 'far' from onset) in order to compare the rate of decline in each with the rate in CAG- individuals. We hypothesise that the rate of progression is not uniform within the prediagnostic period and that it increases as CAG+ individuals approach onset. In addition, the rate of change is faster in CAG+ than in CAG- individuals.

METHODS

Participants

Participants were recruited primarily through the National Research Roster for Huntington Disease Patients and Families. Inclusion criteria were: (1) a parent diagnosed with HD; (2) between the ages of 18 and 65 years; and (3) a non-diagnostic motor examination at the first study visit (Unified Huntington Disease Rating Scale-99³¹ diagnostic confidence level less than 4). All participants completed two study visits, approximately 2.5 years apart. The testing protocol was identical at both visits. Medical history, current medications and history of alcohol and recreational drug use were collected at both visits. Any participants reporting a concurrent neurological illness, major psychiatric diagnosis (eg, schizophrenia, bipolar disorder) or current alcohol or drug abuse were excluded from the analyses. Participants were asked not to disclose their CAG status, if known, to study staff. This study was approved by the local institutional review board (IUPUI IRB Study No 0109-12). All participants provided written informed consent.

Clinical evaluation and study group assignment

Molecular testing of the huntingtin gene was performed³² to determine the number of CAG repeats. Normal controls (NC; n=68) were defined as those having two unexpanded alleles

(<28 CAG repeats). Individuals with at least one expanded allele (>38 CAG repeats) were considered CAG expanded (CAG+; n=39). Subjects whose larger allele contained 28–38 CAG repeats, inclusive, were considered inconclusive and were not used in the analyses (n=10).

Two movement disorder neurologists (JW, XB) administered the motor examination portion of the Unified Huntington Disease Rating Scale-99. Both were aware that the participants were at risk for HD but were blinded to the results of all other study assessments, including the results of huntingtin gene testing. The motor examination was performed for each participant at both study visits. On the basis of the motor examination only, they assigned an overall confidence rating which represented the likelihood that any observed abnormalities represented HD. The ratings were defined as: (0) normal (no abnormalities); (1) non-specific motor abnormalities (less than 50% confidence); (2) motor abnormalities that may be signs of HD (50–89% confidence); (3) motor abnormalities that are likely signs of HD (90–98% confidence); and (4) motor abnormalities that are unequivocal signs of HD ($\geq 99\%$ confidence). CAG+ subjects with a confidence rating from 0 to 3 at their second visit were considered prediagnostic (n=34). Five subjects who were prediagnostic at their first visit became diagnostic (confidence rating of 4) at their second visit. Estimated onset was defined as the age at which a person had a 50% probability of having manifest disease, and the estimated time to onset^{22 33} (TTO) was calculated for each participant at each study visit. The distribution of TTO at the first study visit was reviewed and one subject was removed due to a very large TTO (>3.5 SD from the mean) so that 38 CAG+ subjects were included in the analyses.

Study assessment

The study battery included an assessment of neurocognitive performance, psychomotor speed and saccadic eye movements. All testing was conducted in a private examination room by trained study staff.

Neurocognitive performance and psychomotor speed were evaluated using measures from six tests: (1) Wechsler Adult Intelligence Scale-Revised (WAIS-R)³⁴: arithmetic, picture arrangement and digit symbol subtests; (2) Stroop Colour–Word Interference Task³⁵: word reading, colour naming, interference; (3) Trail Making Test³⁶: parts A and B; (4) WAIS-III³⁷: letter–number sequencing test; (5) California Verbal Learning Test (CVLT)³⁸: total learning, semantic clustering, short delay recall, long delay recall, recognition discriminability; (6) H-scan system³⁹: reaction time (RT) (auditory RT, visual RT, decision RT) and motor speed (movement time (MT), decision MT, alternate button tapping). We also assessed depressive symptomatology using the Center for Epidemiologic Studies Depression Scale (CES-D).

Saccadic eye movement testing was performed as described previously.¹² Briefly, the participant was seated 1 m from a large white screen in front of a bar with vertical and horizontal target lights (light emitting diodes). Three saccadic tasks were administered: anti-saccade (AS) memory guided simple version (MG1) and memory guided complex version (MG2). The vertical and horizontal positions of the participant's pupils were recorded binocularly with two ultra-miniature high speed (250 Hz) video cameras attached to a headband and digitised at 250 Hz for later analysis (Eyelink II, SR Research Ltd, Ottawa, Ontario, Canada; spatial resolution <0.1°). Before each task, the examiner instructed the participant verbally to ensure that the participant understood the instructions. Each of the tasks consisted of 25 trials. After the participant completed the testing procedure, an interactive computerised analysis¹¹ of the right eye position was performed. Current analyses focused on the AS and MG measures (saccadic latency, the SD of saccade latency and percentage of errors) previously reported to demonstrate abnormalities in prediagnostic HD.¹²

Statistical analysis

We tested for group differences in depression at each visit using Fisher's exact test. All analyses evaluated the change in performance of neurocognitive, psychomotor and oculomotor tasks between the two study visits in the NC and prediagnostic CAG+ participants.

To evaluate longitudinal change during the prediagnostic period, we analysed neurocognitive, psychomotor and oculomotor performance using a repeated measures mixed linear model (SAS V.9.13). The model included three terms: (1) a main effect of TTO, indicating a linear relationship between TTO and performance; (2) a main effect of visit, indicating a change in performance between the study visits and perhaps indicating either training/learning or disease progression between the visits; and (3) an interaction between TTO and visit, indicating an effect of TTO on the between visit change in performance. The model also included age, sex and education as covariates when there was a significant effect ($p \leq 0.05$). This analysis included only prediagnostic CAG+ participants.

We also evaluated how the rate of change in prediagnostic CAG+ subjects compared with that in CAG- subjects. To do this, a median split in the TTO distribution was used to define two prediagnostic groups: (1) far from onset (far), defined as those participants whose TTO at the first study visit was greater than 11 years ($n=19$); and (2) near to onset (near), defined as those participants whose TTO was less than 11 years ($n=19$).

The rate of change in the prediagnostic (CAG+) and NC (CAG-) groups for each study measure was calculated for each participant as follows:

$$\text{rate} = (\text{visit 2 measure} - \text{visit 1 measure}) / \text{months between visits}$$

These rates were analysed using analysis of covariance (ANCOVA) to test for group effects (three groups: NC, far, near) with sex, age and education as covariates. For variables with a significant group effect ($p \leq 0.05$), post hoc analysis was performed using two sided t tests of all pairwise comparisons.

For all analyses we employed a nominal significance value ($p \leq 0.05$). We recognise that we are testing multiple outcomes; however, our approach was to review results to identify trends or domains consistently affected in prediagnostic individuals.

RESULTS

The 106 participants included in the analysis completed two visits approximately 2.5 years apart (28.6 ± 5.2 months). The three groups (NC, far, near) did not differ significantly ($p \geq 0.6$) for sex, race, handedness, education or months between study visits, nor was there a significant difference ($p=0.1$) between the near and far groups for the number of CAG repeats (table 1). The groups did, however, differ significantly for age ($p=0.02$), with the far group being significantly younger than the two other groups (table 1). Because of technical difficulties, saccade tasks were completed in only a subset of participants ($n=74$). The prevalence of depression was assessed in our patients using the CES-D. At the first study visit, there was no significant difference between the NC, far and near groups ($p=0.4$). At the second visit, the prevalence was significantly higher in the far group ($p=0.01$).

Repeated measures analysis in CAG+ individuals

Repeated measures analysis was used to examine the main effects of TTO and visit, and the interaction between the two on each of the performance outcomes. Representative plots of the data are shown in figure 1. Each subject's performance at the first and second visits is connected

by a line. For alternate button tapping (figure 1A), subjects require more time to complete 30 round trips as they approach onset, indicating a significant main effect of TTO. A similar trend is not seen for variability of latency of MG1 (figure 1C) or for percentage of errors of MG2 (figure 1E), indicating no significant effect of TTO. The interaction between TTO and visit can be seen by examining the changes from visit 1 to visit 2. For alternate button tapping (figure 1A), the changes for subjects with a larger estimated TTO tend to be relatively flat and become steeper as onset approaches. For variability of latency of MG1 and the percentage of errors of MG2 (figure 1C, E), the changes for subjects with a larger estimated TTO suggest improvement or learning from the first to second visit while the changes for subjects with a smaller estimated TTO suggest a failure to learn from the first visit or reduction in performance that cannot be compensated for with learning effects. To facilitate visualisation of the interaction, the slope of the line in figure 1A, C and E has been plotted as a single point for each subject in figure 1B, D and F, respectively.

The results of the repeated measures analysis are shown in table 2. A significant main effect of TTO ($p \leq 0.04$) was found for subtests of the H Scan (audio and visual RT, MT, decision MT and alternate button tapping), WAIS (picture arrangement, digit symbol and letter number sequencing), CVLT (long delay recall), Stroop (colour naming, word reading and interference), Trail Making (part A) and the AS task (percentage of errors). In all cases, performance was worse in subjects with a smaller TTO than in those with a larger TTO. A significant main effect of visit ($p \leq 0.05$) was found for subtests of the H Scan (alternate button tapping), WAIS (picture arrangement), the MG1 task (percentage of errors, latency and variability of latency) and the MG2 task (percentage of errors). Of these measures, only picture arrangement demonstrated an overall improvement at the second visit, indicating a learning effect. Performance on the other tests with a significant visit effect was worse at the second visit. A significant interaction between TTO and visit ($p \leq 0.02$) was found for subtests of the H Scan (MT and alternate button tapping), the MG1 task (variability of latency) and the MG2 task (percentage of errors). For all four measures, the rate of decline was more rapid as subjects approached onset.

ANCOVA in CAG+ and CAG– individuals

ANCOVA was used to test for differences in the rate of change between the NC, far and near groups. Table 3 shows the raw group means and the p values adjusted for covariates. Significant group differences ($p \leq 0.03$) were found for three measures from the H-Scan (audio and visual RT, and alternate button tapping). For all three measures, post hoc testing demonstrated that the rate of change was significantly greater ($p \leq 0.007$) for the near group compared with the NC. Furthermore, a significantly faster rate of change was found in the near group compared with the far group ($p = 0.007$) for alternate button tapping. For the saccadic tasks, all measures from the MG1 task (percentage of errors, latency and variability of latency) and the percentage of errors from the MG2 task also yielded significant group effects ($p \leq 0.03$). Subsequent post hoc testing found that the rate of change was significantly faster in the near group compared with the NC group ($p \leq 0.008$) for all but the variability of latency of MG1 although a trend was also found for this measure ($p = 0.055$). Furthermore, the rate of change was faster in the near group compared with the far group ($p = 0.04$) for all but the percentage of errors of MG1. Additionally, the far group declined faster than the NC for the percentage of errors of MG1 ($p = 0.02$). No other study measure showed a significant group effect for the rate of change.

DISCUSSION

The identification of potential biomarkers of disease progression in prediagnostic HD is a largely unmet requisite for performing neuroprotective drug trials in CAG+ individuals. We have used two complementary approaches to examine longitudinal changes in prediagnostic CAG+ subjects and to compare these changes between CAG– and CAG+ subjects.

Initial analyses using a repeated measures model with only prediagnostic CAG+ subjects confirmed that performance on a number of neurocognitive, psychomotor and oculomotor tests declines during the prediagnostic period. The results from this study indicate that psychomotor measures (H Scan subtests, digit symbol) are particularly sensitive, and that certain neurocognitive and oculomotor measures are also sensitive to declining performance in the prediagnostic period.

The central hypothesis of the study was that the rate of decline in functioning increases as subjects approach estimated disease onset. This hypothesis was addressed through the interaction term: TTO $\times$ visit. Four subtests (MT, alternate button tapping, variability of latency of MG1 and percentage of errors of MG2) were able to detect a significant change in the rate of decline as subjects approach onset. In all cases, the rate of decline increased as the subjects approached their estimated age of onset. Our results also emphasise the importance of longitudinal studies. For variability of latency of MG1 and percentage of errors of MG2, no cross sectional effect of TTO was detectable. However, it is clear that longitudinal performance changes as subjects approach onset for these two measures. Subjects with a larger estimated TTO tend to perform slightly better at their second visit, indicating a training or learning effect; but those with a smaller estimated TTO perform worse at their second visit, suggesting that they no longer benefit from having done the task previously. It is also noteworthy that all of the measures with a significant TTO $\times$ visit interaction have a motor component, suggesting that motor measures (with or without a cognitive component) may be the most sensitive to detect rate differences during the prediagnostic period.

We also tested the hypothesis that the rate of decline is different between CAG- and CAG+ subjects. The CAG+ subjects were dichotomised into either a far from or near to onset group. Of the seven subtests with a significant ANCOVA test ($p \leq 0.05$), post hoc tests revealed a difference between the NC and near groups for six of the subtests. For the seventh subtest (variability of latency of MG1), a trend was also found ($p = 0.055$). Only the percentage of errors of MG1 was sufficiently sensitive to detect a difference between the NC and far groups. Interestingly, this measure did not detect a significant difference in the rate of decline during the prediagnostic period using either method, suggesting that the rate of change is different between CAG- and CAG+ subjects but that the rate is constant throughout the prediagnostic period.

ANCOVA confirmed the results from the repeated measures analysis that supported a changing rate of decline during the prediagnostic period for alternate button tapping, variability of latency of MG1 and percentage of errors of MG2. The only discrepancies between the two methods were with MT and latency of MG1. Further examination of these data suggest that a difference in the rate of decline in MT is subtle and that dichotomisation of the sample increased variability so that differences could not be detected. On the other hand, it appears that the significant difference found in latency of MG1 is likely due to a few subjects, and a larger sample may be required to have sufficient power to test this hypothesis.

These results provide a functional correlate to longitudinal anatomical findings. Aylward *et al*⁴⁰ reported significantly smaller striatal volume cross sectionally in subjects up to 20 years before onset; however, the rate of striatal atrophy was significantly increased only 10 years prior to onset. Many previous cross sectional studies detected performance differences during the prediagnostic period^{4–14,22}; however, fewer longitudinal studies have been performed and differences in the rate of change during the prediagnostic period have not been consistently reported.^{18,23–30} Our data would appear to suggest that the differences in rates are subtle but can be detected with particular measures. As seen from the ANCOVA, the most significant differences in rate of change are between the NC and near groups, indicating that the most rapid decline occurs close to onset. Furthermore, by directly plotting the rate of change for

each subject against TTO at the first visit (figure 1), it appears that for alternate button tapping and the percentage of errors of MG2 the rate of decline increases only as subjects are within approximately 10 years of their estimated age of onset. However, for the variability of latency of MG1, the rate of decline appears to increase earlier in the prediagnostic period. Further work is required to see if this pattern is consistent but it may indicate that saccadic measures are more sensitive in detecting differences in rate of change early in the prediagnostic period; however, they may not be more sensitive than other measures when examining the entire prediagnostic period.

While in many instances CAG+ individuals further from their estimated onset do not appear to decline more rapidly than CAG-, this does not imply an absence of pathology. Others have noted the likelihood of compensatory mechanisms sufficient to mask the behavioural effects of underlying pathology early in the prediagnostic period. This study does not use methods to investigate underlying neural integrity (eg, MRI, fMRI, EEG, etc) and thus cannot test whether there is an absence of pathology in our subjects or neuronal compensation that masks pathological changes.

This study had several strengths and weaknesses. One strength was that all study participants had a parent with HD and thus were at risk for HD. This generates groups that have greater matching for unmeasurable factors compared with a study in which the CAG- group is not at risk for HD. In addition, all subjects completed a uniform study visit that evaluated a number of domains reported to be affected early in disease progression. The study also had several weaknesses. The size of the sample is similar to that of previous studies but is still relatively modest to detect small differences in rates of change. Furthermore, the sample of CAG+ individuals tended to have a smaller number of expanded repeats with fewer subjects having greater than 50 repeats. As a result, we have limited power to test whether those with a larger number of CAG repeats (ie, >50 CAG) have more rapid rates of decline compared with those having the more typical number of repeats (39–50 CAG repeats). We collected data regarding depression using the CES-D and found that depressive symptomatology was significantly higher in the far group than the two other groups at the second visit. One possible explanation may be that as subjects approach onset (near group), the depressive symptoms worsen and they seek medical attention to alleviate its effects. Unfortunately, we were not able to assess this explanation because we did not ask subjects if they had sought medical care for depression. Finally, both a strength and a weakness of the study was that the CAG+ individuals were distributed throughout the prediagnostic continuum as estimated by their TTO. This allowed the use of TTO as a continuous variable and evaluated a linear relationship between TTO and performance; however, it also likely resulted in extensive heterogeneity within each group when the CAG+ participants were divided into near and far groups.

We are currently collecting data for a third time point in these subjects. We will evaluate whether these new data provide improved model fitting to better estimate the rate of disease progression across study variables in a sample of subjects who are either prediagnostic or in the early stages of clinically diagnosable disease. We anticipate that these data will further improve our ability to identify sensitive and specific biomarkers in the early stages of disease progression.

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Figure 1.

Performance of CAG+ subjects. Progression is shown both by connecting a subject's performance at each study visit with a line versus time to onset (TTO) at each visit (A, C, E) and as the change in performance/TTO year versus TTO at the first study visit (B, D, F). (A, B) Alternate Button Tapping; (C, D) variability of latency of memory guided simple version of the saccadic task (MG1); (E, F) percentage of errors of memory guided complex version (MG2) of the saccadic task.

Table 1

Participant demographics

	NC	Far	Near
No of participants	68	19	19
Age at first visit (years)*	45.2±8.7	39.5±9.2	47.7±10.8
Time between visits (months)*	28.2±4.1	29.5±7.0	29.1±6.6
Education (years)*	15.6±2.8	15.5±1.9	15.6±3.4
Sex (M:F)	19:49	6:13	7:12
Race (% Caucasian)	98.5	100	100
Handedness (% right)	91.2	89.5	89.5
CAG repeats*		41.7±2.7	43.4±4.0
Estimated time to onset computed from first visit (years)*		18.2±4.7	8.1±1.7

NC, normal controls.

* Mean±SD.

Table 2

Results of repeated measure mixed model

Test	Repeated measures		
	TTO	Visit	TTO × visit
H scan			
Audio reaction time	0.01	NS*	NS
Visual reaction time	0.004	NS	NS
Decision reaction time	NS	NS	NS
Movement time	0.0007	NS	0.009
Decision movement time	0.0003	NS	NS
Alternate button tapping	0.005	0.02	0.02
WAIS-R/WAIS III			
Arithmetic	NS	NS	NS
Picture arrangement	0.02	0.05	NS
Digit symbol	0.02	NS	NS
Letter number sequencing	0.03	NS	NS
CVLT			
Total learning	NS	NS	NS
Semantic clustering	NS	NS	NS
Short delay recall	NS	NS	NS
Long delay recall	0.04	NS	NS
Recognition discriminability	NS	NS	NS
Stroop			
Colour naming	0.004	NS	NS
Word reading	0.004	NS	NS
Interference	0.04	NS	NS
Trail making test			
Part A	0.02	NS	NS
Part B	NS	NS	NS
Anti-saccade			
Percentage of errors	0.0001	NS	NS
Latency	NS	NS	NS
Variability of latency	NS	NS	NS
Memory guided 1			
Percentage of errors	NS	0.05	NS
Latency	NS	0.03	NS
Variability of latency	NS	0.005	0.01
Memory guided 2			
% Of errors	NS	0.0003	0.0008
% Of missed flashes	NS	NS	NS

CVLT, California Verbal Learning Test; TTO, time to onset; WAIS-R, Wechsler Adult Intelligence Scale-Revised.

* NS (p>0.05).

Table 3

Results of ANCOVA with three groups

Test	Mean $\pm$ SD		p Values			
	NC	Far	Near	Group	NC vs far	NC vs near
H scan						
Audio reaction time	-0.00038 ± 0.00077	-0.00022 ± 0.00062	0.00031 ± 0.0012	0.007	0.4	0.002
Visual reaction time	-0.00016 ± 0.00064	$5.8E-05 \pm 0.00067$	0.00029 ± 0.00094	0.03	0.5	0.007
Alternate button tapping	-0.011 ± 0.076	-0.0042 ± 0.063	0.053 ± 0.13	0.005	0.7	0.002
Memory guided 1						
% of errors	-0.20 ± 0.40	0.34 ± 0.78	0.53 ± 0.87	0.005	0.02	0.003
Latency	-0.015 ± 1.94	0.26 ± 2.41	2.19 ± 3.13	0.03	0.8	0.008
Variability of latency	0.47 ± 2.55	-0.13 ± 2.38	1.91 ± 2.77	0.03	0.2	0.055
Memory guided 2						
% of errors	-0.036 ± 1.16	-0.25 ± 1.16	0.86 ± 0.92	0.01	0.9	0.006
NC, normal controls.						0.01