Published in final edited form as:

Mov Disord. 2010 July 30; 25(10): 1343–1349. doi:10.1002/mds.22692.

Abnormal explicit but not implicit sequence learning in pre-manifest and early Huntington's disease

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Abstract

Learning may occur with or without awareness, as explicit (intentional) or implicit (incidental) learning. The caudate nucleus and the putamen, which are affected early in Huntington's disease (HD), are thought to be essential for motor sequence learning. However, the results of existing studies are inconsistent concerning presence/absence of deficits in implicit and explicit motor sequence learning in HD. We assessed implicit and explicit motor sequence learning using sequences of equivalent structure in fifteen individuals with a positive HD genetic test (7 pre-manifest; 8 early stage disease) and 11 matched controls. The HD group showed evidence of implicit motor sequence learning, whereas explicit motor sequence learning was impaired in manifest and pre-manifest HD gene carriers, with progressive decline with progressive disease. Explicit sequence learning may be a useful cognitive biomarker for HD progression.

Keywords

Huntington's disease; Manifesting; Pre-symptomatic; Explicit sequence learning; Implicit sequence learning; Serial reaction time task

Knowledge acquisition, storage and application are elementary for adaptive behaviour and survival. Learning may occur with or without awareness, referred to as explicit (intentional) or implicit (incidental). Numerous brain areas including the putamen and caudate, the prefrontal cortex, primary, supplementary motor and anterior cingulate cortices are involved in processing and learning of motor sequences.¹⁻³ Neurological disorders affecting these brain regions may present with motor sequence learning impairment.

Huntington's disease (HD) is a neurodegenerative trinucleotide repeat disorder characterized by early striatal degeneration.⁴ Biomarkers of disease progression are fundamental to evaluate clinical trials in pre-manifest and early stage HD. Brain imaging studies have demonstrated changes as early as ten years prior to onset. Similarly, subtle subclinical behavioural changes are being investigated.^{5,6} A dissociation between explicit and implicit motor sequence learning (EL and IL), with impaired EL in the presence of intact IL, has been demonstrated for symptomatic HD patients³, although others found impaired IL on serial reaction time tasks (SRT).^{7,8} A proposed explanation of this discrepancy: Caudate degeneration, a very early feature of HD, may be responsible for deficits in EL; whereas putaminal dysfunction considered to occur later in HD, may underlie the intact IL on the SRT.³ However, with growing evidence that HD pathology also involves the putamen from very early pre-manifest stages^{9,10}, an alternative hypothesis is that both IL and EL are impaired in HD. To assess this we studied genetically proven pre-manifest HD gene

mutation carriers, early disease HD patients and matched controls for both IL and EL, with tasks using equivalent sequence structures.

Methods

Participants

Fifteen individuals (3 male) with molecularly-proven HD (Table 1) aged 28-64 ($M = 41.7$, $SD = 6.5$) were recruited from the HD clinic at the National Hospital for Neurology and Neurosurgery. Motor, psychiatric and cognitive symptoms were assessed using the Unified Huntington's Disease Rating Scale (UHDRS).¹¹ Time to symptom onset was calculated according to Langbehn *et al*¹² using a probability of onset of 60%.

Seven HD gene carriers who had not yet developed diagnostic motor symptoms were classified as pre-manifest (pre-HD). Eight HD gene carriers were classified as early manifest (early HD) since they had developed early motor symptoms. None had significant cognitive impairment (Mini-Mental State Examination (MMSE)¹³ scores > 27), except two with an MMSE score $= 26$ (mild cognitive impairment). However, we appreciate that the MMSE may not be the best instrument to rule out cognitive impairment in HD. All HD subjects were also screened for clinical depression (scores > 18) on the Beck Depression Inventory (BDI).¹⁴ One early HD patient obtained a BDI score $= 23$ (moderate to severe depression); all others were non-depressed. None were taking medication for HD.

Eleven healthy volunteers (5 male) aged 27-56 ($M = 39.45$, $SD = 9.22$) participated. None had any neurological disorder or history of psychiatric illness, head injury, drug or alcohol abuse. Informed consent was obtained prior to participation.

Implicit sequence learning

Two second order conditional sequences, SOC1 = 3-1-4-3-2-4-2-1-3-4-1-2 and SOC2 = 4-3-1-2-4-1-3-2-1-4-2-3 were used in the probabilistic SRT. Approximately half the participants in each group, trained on SOC1 as training sequence, the remainder SOC2. During the experiment, on any one trial the target location was specified by the assigned probable sequence (85%) or by the improbable sequence (15%). All participants performed the IL task prior to the EL task. The IL task comprised 12 blocks, 100 trials each, with a four-choice SRT task. Four boxes were arranged horizontally along the middle of a computer screen and, on each trial, participants reacted to the target location in one of the four boxes as quickly as possible by pressing the corresponding button on a four-button response box using the first four fingers of their dominant hand. The instruction was to respond as fast and as accurately as possible. Each block began at a random point in the sequence. A trial ended when the correct key was pressed, at which time the target disappeared. The next target appeared after 400 msec. Response latencies were measured.

Explicit sequence learning

In the EL task participants were informed that they had to learn a sequence of target locations by trial-and-error (e.g. SOC 3 = 2-4-2-1-3-4-1-2-3-1-4-3). Sequence length was not disclosed. The sequence repeated unchanged throughout the task. The first target location was highlighted on the computer screen. Participants were instructed to try to work out the next location by pressing one of the keys corresponding to the three possible target locations. If incorrect there was an auditory feedback, the highlighted stimulus remained in the same location, and participants had to give another choice. This process was continued until the response was correct. To successfully complete a block, correct responses to 10 repetitions of the 12-item sequence were required.

The total number of correct trials on the first attempt was calculated. The task ended either when the criterion of 75 % total errorless responses was reached or, if not achieved, after completion of 10 blocks. Approximately half the participants in each group trained on SOC3; the remainder on SOC 4 (=3-4-3-1-2-4-1-3-2-1-4-2)¹.

Other tests

Specific aspects of cognition, particularly executive function and immediate span and working memory were also assessed in HD patients (see Table 1).

Results

Controls and pre and early HD patients did not differ in terms of demographic information (Table 1).

Implicit sequence learning

Overall mean RTs significantly differed across the three groups [$F_{(4.3, 93.8)} = 3.87, p = .01$] and as expected were significantly longer in the two HD groups relative to controls (early HD, $t_{(15)} = -2.36, p = .03$; pre-HD, $t_{(8.5)} = -3.28, p = .01$). Therefore, prior to the following statistical analysis of learning for each participant raw RTs were converted to Z scores.

Learning across blocks. RTs—Figures 1a-c depict mean Z_{RT} s obtained over the training phase, plotted separately for the three groups and for each type of target location, probable or improbable. First, to establish whether learning was present and to compare patterns of learning across blocks and in the three groups, an ANOVA was performed on mean Z_{RT} with Probability (probable vs. improbable) and Block (1-12) as within-subject variables and Group (control vs. pre-HD vs. early HD) as a between groups variable. This revealed a significant main effect of Probability [$F_{(1, 23)} = 11.17, p = .003$] indicating faster responses to probable compared to improbable targets, indicating learning. There was a significant main effect of Block [$F_{(4.7, 106.9)} = 3.15, p = .01$] and a significant interaction between Group $\times$ Block [$F_{(22, 253)} = 1.57, p = .05$]. The main effect of Group and all other interactions were non-significant. For composite measures of learning across all blocks see online supplements.

Correlations—Composite measures of learning across all blocks were obtained by calculating a difference score for each participant (Z_{RT} scores for improbable trials - Z_{RT} scores for probable trials) at each block and then across all blocks. To explore any relationship between learning and disease severity in HD subjects, Pearson's correlations were calculated between mean Z_{RT} difference scores across blocks and UHDRS, mean CAG repeat length and (for pre-HD patients only) years to disease onset. These correlations were performed for a) all HD patients and b) for early and pre-HD groups separately. None of these correlations were significant. For the early HD group, digits forward showed a negative association with the mean Z_{RT} difference scores which approached significance ($r = -.70, p = .06$). All other correlations between IL and tests of executive functioning and working memory were not significant.

Explicit sequence learning

Learning across blocks, total errorless responses per block—Figure 2 depicts mean total number of errorless responses across 10 blocks of the EL task, plotted separately for the three groups. An ANOVA with mean total errorless responses with Block (1-10) as a within-subject variable and Group as a between groups variable, revealed a significant main effect of Block [$F_{(3.0, 68.6)} = 36.79, p < .000$], indicative of learning, and a significant main

effect of Group [$F_{(2, 23)} = 5.05$, $p = .02$], reflecting significant overall group differences in EL. The interaction between Group $\times$ Block was not significant.

In light of the significant main Group effect, overall mean total number of errorless responses (collapsed 10 blocks) was calculated and plotted separately for the three groups (Figure 3). Independent samples t -tests were performed to compare overall mean total errorless responses across the three groups. Controls achieved significantly more total errorless responses compared to pre-HD patients [$t_{(16)} = 1.93$, $p = .04$, 1-tailed] and early HD patients [$t_{(17)} = 3.12$, $p = .01$]. There was no significant difference between pre and early HD patients [$t_{(13)} = 1.04$, $p = .32$]. Although significantly reduced relative to controls, EL learning was not entirely abolished in HD gene carriers because, for all three groups overall mean total number of errorless responses was significantly better than chance (40 total errorless responses per 120 items) [controls, $t_{(10)} = 14.54$, $p < .0001$, pre-HD patients, $t_{(6)} = 8.07$, $p < .0001$, early HD patients, $t_{(7)} = 6.12$, $p < .0001$].

Blocks to criterion—The mean number of blocks performed to reach the 75% criterion for the early HD patients ($M = 7.88$, $SE = 1.27$) was significantly greater than for controls ($M = 3.82$, $SD = 2.56$) [$t_{(17)} = -2.88$, $p = .01$], while there was no significant difference between pre-HD ($M = 5.00$, $SE = 1.27$) and controls ($t < 1$) or between the two HD groups [$t_{(13)} = -1.59$, $p = .14$].

Correlations—Correlations were calculated between the overall mean total number of errorless responses, blocks to criterion and UHDRS, mean CAG repeat length and years to disease onset, and measures of executive functioning and working memory. Again, correlations were performed for a) all HD patients and b) for early and pre-HD groups separately. For all HD gene carriers, worse EL (indexed by a greater number of blocks to reach criterion) was significantly associated with increased CAG repeat length ($r = .4$, $p = .05$). For the pre-HD group, UHDRS ratings had a marginally significant negative relationship with the mean total number of errorless responses ($r = .64$, $p = .06$). For early HD patients, all correlations were non-significant. For the early HD group, the mean total number of errorless responses had a significant positive relationship with category ($r = .84$, $p = .02$) and letter ($r = .76$, $p = .04$) fluency and a marginally significant positive relationship with the digit span backward test ($r = .62$, $p = .09$). All other correlations were not significant.

Maximum number of consecutive errorless responses per block

(See online supplements for results and figure)

Proportion of participants reaching criterion

(See online supplements for results and figure)

Discussion

We assessed implicit and explicit sequence learning in fifteen individuals (seven pre-manifest and eight early affected patients) carrying the HD genetic mutation. We found evidence of IL on the probabilistic SRT in the HD groups. In contrast, EL sequence learning by trial and error was impaired in pre-manifest and early stage HD relative to controls. Differences between the two HD groups did not reach significance for the majority of the explicit measures, which may be due to the small sample sizes in the patient sub-groups.

Implicit sequence learning in Huntington's disease

All three groups, healthy controls, pre-HD and early HD patients, demonstrated evidence of IL of a probable sequence and the magnitude of learning was similar in all groups. There was no relationship with clinical scores including disease severity as rated on the UHDRS.

Our findings demonstrate that - despite a significant slowing of overall RTs - IL was similar in HD patients and controls', in line with previous findings of IL retention in HD^{3,15}, although others found impaired SRT learning in HD.^{7,8} However, the SRT paradigms used in these studies differed from our present task as they employed a deterministic SOC version of the SRT, whereas we chose a probabilistic sequence. Nevertheless, use of deterministic instead of probabilistic SRT cannot be the sole determining factor: Brown *et al.*³ also used a deterministic SRT but similar to us found intact IL on the SRT in HD patients. Other methodological differences such as length and exact structure of the sequence, the response-stimulus interval and the HD severity too may be important factors. Use of probabilistic SRT has advantages over fixed deterministic SRT¹⁶, and using this approach, we found evidence of IL in HD.

IL assessment on a deterministic SRT task using fMRI¹⁵ revealed a significantly slower RT in HD compared to controls. The group $\times$ condition interaction was not significant, indicating equivalent IL in the HD and control groups in line with our results.

Impaired explicit sequence learning in early Huntington's disease

We observed some level of EL in all three groups, as suggested by a number of errorless responses above chance in all groups. Nevertheless, controls achieved significantly more total errorless responses and more maximum consecutive errorless responses relative to both, pre-manifest and early HD patients. In addition, early HD patients on average required significantly more blocks (mean 7.88) to reach the 75% criterion compared to controls (mean 3.82 blocks). Pre-HD patients required on average 5 blocks to reach the criterion. Our findings indicate impaired EL in HD, consistent with previous reports.¹⁷ Furthermore, our results show the progressive nature of EL impairment with progressive disease. While Brown *et al.*'s³ main cohort of interest was a group of disease manifesting HD patients, we studied both pre-manifest and early disease patients. In our study the mean UHDRS was 2.9 (pre-HD) and 17.9 (early HD), compared to 41.8 in Brown's main cohort. While in our study, 86% of pre-HD patients and 50% of early disease patients, only 3 of 16 of Brown's³ patients (18%) reached the 75% criterion within ten blocks. Our findings were significant with less early HD patients reaching criterion compared to normal controls. Notably, all our patients (12/12) completed the 10 blocks successfully, albeit a more difficult sequence of 12-items, while three patients in Brown's study abandoned the task prematurely, despite an 'easier' 8-item sequence. In addition, several other factors may explain why Brown *et al.* saw a more striking impairment of EL in disease manifesting HD patients relative to the present study. For example, Brown's HD patients were less well educated with an average of 9.3 years of education compared to 13.5 and 14.1 in our presymptomatic and early disease groups. Brown's patients took a variety of HD medications including neuroleptics, benzodiazepines and SSRIs whereas our patients were HD drug naïve. Interestingly, in addition to their main cohort of HD patients, Brown *et al.* also studied a subgroup of three presymptomatic gene carriers, and unlike the present study, this subgroup performed normally on the EL task. It is possible that the Brown's EL task was too easy to detect an EL impairment their presymptomatic patients.

In a recent PET study¹⁸ EL of an 8-item motor sequence was impaired in 11 pre-manifest HD subjects (mean CAG repeat length 41.6; mean UHDRS 7.6). There was increased activation in the caudate and orbitofrontal cortex, interpreted as possible compensatory

mechanisms for deficient activation in the dorsolateral prefrontal cortex. This is in line with our findings and with the proposal that the caudate plays a role in EL.

However, given the evidence that the putamen and the caudate are involved in both IL and EL,¹⁹ and that both nuclei are affected early in HD^{9,10}, the question arises why there was impairment of EL but not IL. One explanation may be that EL more than IL relies on other cortical areas such as prefrontal cortices¹⁹ which are also affected early in HD^{20,21}. This hypothesis is supported by our finding that in the early HD group better performance on the EL (but not IL) task was related to better performance on some of the 'prefrontal' tests of executive function and working memory.

A second possibility is that, in the present study, both pre and early HD patients showed impaired EL because successful performance relied not only on learning with intention but also on learning with corrective feedback (i.e. by trial and error). Both imaging learning studies in healthy humans^{22,23} and learning studies in PD²⁴ demonstrate that the striatum is essential for learning with corrective feedback. Even within the caudate and other striatal structures, areas activated during classification learning with feedback can be subdivided into regions associated with actual learning (body and tail of the caudate and putamen) and with processing of feedback (head of caudate and ventral striatum).²⁵ Therefore, possibly, during the EL task, HD patients - who have both putamen and caudate dysfunction - were either impaired at actual learning and the processing of feedback or selectively impaired at feedback processing but had intact learning. Future studies of EL in HD patients could examine this question directly by adopting an explicit sequence learning task that does not require the processing of corrective feedback.²⁶

A final possible explanation is that HD patients were impaired at EL as the result of greater proactive interference in HD patients relative to controls, caused by the transfer of information from the IL to the EL task. Future studies could test this possibility directly although it has been shown previously that HD patients do not show proactive interference during associative learning.²⁷

Explicit learning as a biomarker of disease progression in Huntington's disease

Clinical diagnosis in a patient at risk for HD, by virtue of a positive family history or a positive predictive genetic test is currently based on presence of motor signs. At the time of clinical diagnosis, there is already overt caudate and putamen atrophy.⁴ Ideally, introduction of neuroprotective treatments should occur at an earlier, pre-manifest disease stage. For evaluation of neuroprotective agents in clinical trials, biomarkers are required which objectively reflect pathogenic processes and treatment response.²⁸ Proposed biomarkers include MRI changes, present at least 10 years before estimated clinical onset^{5,10}. Cognitive measures like EL may also be of interest, and our data suggest not only that EL declines with progressive disease, but that impairment is already present in pre-manifest stages with a mean of 18 years to predicted disease onset¹². Further studies investigating larger sample sizes will help determining the usefulness of EL as biomarker.

In summary, we have found evidence of intact IL but impaired EL in manifest but also pre-manifest HD gene mutation carriers. Our data suggest decline of EL with advancing disease suggesting that EL measures may be useful biomarkers of HD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Footnotes

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Author roles Conception (MJ, LW, KB, JCR, SJT), Organization (SAS, LW, SH, SJT, KB, JCR), Execution (SAS, LW, SH); Statistical Analysis (LW, MJ); Manuscript Writing of the first draft (SAS, LW, MJ) and review and critique (KB, SH, JCR, SJT).

Author note We are grateful to all the participants and we would like to thank E. Wild for his help with patient recruitment and C. Baader for helpful comments.

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Full financial disclosures

Disclosure of SAS: Sources of support: Brain Research Trust, Novartis Foundation, University Luebeck, Germany (Employment);

Disclosure of LW: 2006-2009 Postdoctoral Research Fellow (Parkinson's Disease Society Postdoctoral Fellowship, £152, 261 over 3 years) Sobell Department, IoN, NHNN, UCL.

Disclosure of KB: honoraria/ financial support to speak/attend meetings from GSK, Ipsen, Merz, and Orion pharma companies.

Disclosure of SH: Employment: June 2003 - Sep 2008, employed by UCL, Institute of Neurology Funded (i.e. salary paid) by CHDI Inc.; Sep 2008 - present, employed by Camden and Islington NHS Foundation Trust (and paid a salary by them), concurrently a student at UCL.

Disclosure of JR: Sources of support:

2005-2010	£700k	Functional Connectivity of the motor system in healthy subjects and in patients with movement disorders or stroke <i>Medical Research Council, UK. G0500258</i>
2006-2009	£175k	Role of cortical plasticity in deep brain stimulation for primary and secondary dystonia. <i>Action Medical Research AP1068</i>
2007-2009	£10.4	Deep Brain Stimulation v. ablative lesions for Parkinson's disease. <i>International Joint Projects, Royal Society, UK</i>
2007-2009	£110k	Can theta burst stimulation accelerate re-learning of impaired wrist and hand movements early after stroke? <i>The Stroke Association TSA 2007/06</i>
2007-2009	£12k	Exploring abnormal plasticity in genetic and psychogenic dystonia. The Royal Society International JointProjects Grant
2007-2010	£250k	The human visuomotor grasping circuit: distinct contribution of parietal and frontal areas and their interactions with the primary motor cortex. [Joint applicantwith Prof R Lemon] <i>Wellcome Trust, UK (083450)</i>
2008-2009	£12.6k	Enhancing the effect of physical therapy for motor impairment after stroke with Theta Burst Stimulation (TBS). <i>Rosetrees Foundation, UK</i>
2008-2012	£243k	Restorative Plasticity At Corticostriatal Excitatory Synapses: an <i>FP7 Collaborative Project (222918)</i> , <i>Leader Dr P Calabresi, Rome. (Share of Euro 4.2 million)</i>
2009-2013	£237k	PLASTICISE: an <i>FP7 Collaborative Project (223524)</i> , <i>Leader Dr J Fawcett, Cambridge. (Share of Euro 4 million)</i> ;

Disclosure of ST: Employment: UCL; funding sources for research are MRC, Wellcome Trust, CHDI (Cure HD Foundation), NIHR and the Brain Research Trust.

Disclosure of MJ: Funding: Parkinson's Disease Society UK, Fondation Caja Madrid, Spain Royalties: Elsevier re book The Bereitschaftspotential co-edited with Mark Hallett; Employment: HEFCE funded UCL IoN

¹SOCS 1 & 2 and SOCS 3 & 4 are different but parallel pairs of SOCS. For counterbalancing purposes, for half of the participants in the incidental sequence learning task, SOCS 1 & 2 were substituted by SOCS 3 & 4 and for those participants, for the intentional learning task, SOCS 3 & 4 were substituted for SOCS 1 & 2.

Disclosure: The authors have no conflicts of interest. This research was supported by the Astor Studentship by the Brain Research Trust, UK (SAS), a Career Development fellowship from the Parkinson's Disease Society, UK (LW), The Wellcome Trust (JCR) and an RO1 grant from the National Institute of Neurological Disorders and Stroke, National Institute of Health, USA (MJ). The Dementia Research Centre is an Alzheimer's Research Trust Co-ordinating Centre. SMDH is funded by CHDI Inc. This work was undertaken at UCLH/UCL, which received a proportion of funding from the Department of Health's NIHR Biomedical Research Centres funding scheme.

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Figure 1a.

Mean Z_{RT} across 12 training blocks for the incidental sequence learning task for controls for the probable and improbable trials. Error bars represent standard errors.

Figure 1b.

Mean Z_{RT} across 12 training blocks for the incidental sequence learning task for the pre-HD group for the probable and improbable trials. Error bars represent standard errors.

Figure 1c.

Mean Z_{RT} R across 12 training blocks for the incidental sequence learning task for early HD patients for the probable and improbable trials. Error bars represent standard errors.

Figure 2.

Mean number of total errorless responses across blocks for the intentional sequence learning task, plotted separately for early and pre-HD patients and controls. Error bars represent standard errors. The horizontal dashed lines represent task criterion and chance level.

Figure 3.

Overall mean number of total errorless responses for the intentional sequence learning task, plotted separately for early and pre HD patients and controls. Error bars represent standard errors. Asterisks indicate where the comparison between HD patients and controls was significant. A double asterisk indicates $p < .05$ (2-tailed), whereas a single asterisk indicates $p < .05$ (1-tailed).

Table 1

Demographic information for early, pre HD patients and controls and clinical characteristics of patients.

	Early HD (<i>n</i> = 8)		Pre HD (<i>n</i> = 7)		CONTROL (<i>n</i> = 11)		<i>p</i>
	Mean	S.D.	Mean	S.D.	Mean	S.D.	
Age	46.13	8.27	39	7.94	39.45	9.22	.20
Years of education	13.50	2.39	14.14	1.95	15.00	3.44	.52
Mini Mental State Examination	28.00	1.60	29.21	0.70	29.18	0.98	.07
Pre morbid IQ	109.25	9.18	106.00	7.07	105.57	5.74	.59
Current IQ	123.50	5.21	124.00	4.86	124.73	3.90	.86
Beck Depression Inventory	7.75	7.35	5.86	5.06	4.14	2.88	.34
	Mean	S.D.	Mean	S.D.			
CAG repeat	44.25	1.49	41.43	1.27			
Unified Huntington's Disease Rating Scale	17.88	8.87	2.86	2.61			
Years to HD onset			18.19	9.29			
Stroop: interference	38.33	7.53					
Score on the digit span test: digits forward	13.17	2.86					
Score on the digit span test: digits backward	11.33	4.37					
Verbal fluency: category fluency	19.50	7.50					
Verbal fluency: letter fluency	33.83	13.24					