Chapter 3

Longitudinal pilot-study of Sustained Attention to Response Task and P300 in manifest and premanifest Huntington's disease

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In press Journal of Neuropsychology

Abstract

Background Earlier research has found cross-sectional attentional control deficits in manifest Huntington's disease (HD) using neuropsychological testing combined with simultaneous P300 registration. In the current pilot-study we investigate attentional control in premanifest and manifest HD over a three-year follow-up period.

Method Five manifest HD (MHD), 9 premanifest HD (PMHD) and 12 control subjects were included. Sustained Attention to Response Test (SART) and P300 registration resulted in number of errors, reaction time (RT), and P300 amplitude and latency. RT change patterns surrounding No-go trials were also investigated. Within-subject differences were tested using paired-samples t-tests and between-group results with ANCOVA on delta scores (follow-up - baseline scores).

Results MHD made more errors and were slower than controls and PMHD. Longitudinally, MHD showed an overall RT increase and a specific slowing on trials preceding a correct No-go trial. The latter was also seen in PMHD. P300 latency prolongation was found for controls on No-go and for MHD on Go trials. Directly preceding a correct No-go, MHD became significantly slower over time than controls and PMHD.

Conclusions Over three-years MHD subjects became slower on the SART and showed a prolongation of P300 latency on specific SART trials. Specific slowing of performance over time was also seen in PMHD, suggestive of compensatory mechanisms in this group.

INTRODUCTION

Huntington's disease (HD) is a neurodegenerative disease caused by a gene mutation located on chromosome 4[1]. Its clinical manifestation is heterogeneous, with symptoms and signs occurring in three domains: motor, psychiatry and cognition[2]. Attentional deficits in HD patients have been widely demonstrated[3 4 5]. In premanifest HD subjects, i.e. gene carriers without overt clinical symptoms, differences in attentional processing compared to controls have also been found[6], but with inconsistent results[7 8]. Reports on longitudinal change in attentional functioning in premanifest HD are few[9 10 11], and again contradictory results have been found[12 13].

A practical test to investigate attentional processing is the Sustained Attention to Response Task (SART)[14], a simple Go/No-go task with little motor involvement. The P300, an event-related potential (ERP) that can be deduced from the EEG, is proposed to be an electrophysiological substrate of attentional and inhibitory processes[15 16]. In combination, these two assessments have demonstrated ability to detect lapses in attention[17].
Hart and colleagues[18] combined the SART with a simultaneous P300 registration to investigate attentional functioning in both a manifest and a premanifest HD group cross-sectionally. They demonstrated that attentional control was deficient in manifest HD subjects, apparent in the inability to directly resume task requirements after having made an error. The manifest subjects showed higher error rates corroborated by abnormalities in the P300 signal. While the attentional control deficit in manifest HD was evident, the performance of the premanifest HD group did not differ from that of controls, and no P300 abnormalities were found.

Recent MRI studies reported early brain changes involving grey and white matter[19 20] in premanifest gene carriers even far from expected disease onset. This raises the possibility that these changes can also be measured with functional assessments, such as P300. Indeed, differences in ERPs between premanifest HD subjects and controls have been found[21]. A majority of these studies have found reduced neurophysiologic measures in the absence of abnormal clinical performance in the premanifest groups. This coincides with findings in MRI studies where pathological changes in premanifest HD gene carriers are seen before onset of clinical symptoms[20].
To date, one longitudinal study has been performed using electrophysiological assessment in HD. Here, somatosensory evoked potentials were studied in a group of manifest HD subjects. The amplitude of these potentials demonstrated progressive decline over the two year follow-up period[22]. To our knowledge, no longitudinal electrophysiological research has been performed in premanifest HD subjects yet.

The current pilot-study aimed to investigate attentional deficits in premanifest and manifest HD subjects longitudinally. Observed early brain changes in preman-

ifest HD literature lead us to expect possible longitudinal change for SART error scores and P300 characteristics over the three year interval in this group. For the manifest group we expected to find abnormalities similar to those found earlier by Hart and colleagues: longer reaction time, more errors, and a lower No-go P300 amplitude than controls and premanifest HD subjects. Furthermore, due to the progressive nature of HD we expect a longitudinal worsening of these outcome values.

METHODS

Participants

Five manifest (MHD), 10 premanifest (PMHD), and 13 control subjects participated in this pilot-study and were tested with a three-year interval using the same tests. All subjects completed the baseline and follow-up visit, with a mean follow-up time of 36.7 months. One PMHD and one control subject were excluded from longitudinal analyses due to excessive muscle artefacts visible during the ERP registration. Eventually, data of 5 MHD, 9 PMHD and 12 control subjects were analyzed. None of the PMHD subjects converted to manifest HD over the study period. All subjects were grouped at visit 1 and were subsequently analyzed in this group at follow-up.

All participants were recruited from our outpatient neurology clinic. The controls were gene-negative relatives. Genecarriers were considered premanifest if they had a CAG expansion of $>$39 and a total motor score (TMS) of 5 on the Unified Huntington's Disease Rating Scale (UHDRS)[23]. Disease burden was calculated using the formula 'age(CAG-35.5)'[24]. Exclusion criteria for all subjects were major psychiatric disorder, neurological co-morbidity, a score of $\leq$25 on the Mini Mental State Examination (MMSE)[25] and medication with known effects on the P300 (e.g. neuroleptics). The study was approved by the local medical ethical committee and all participants gave written informed consent (according to the declaration of Helsinki). Subjects underwent neurological examination including the complete UHDRS, P300 and SART assessment on both baseline (visit 1) and follow-up visit (visit 2). The MMSE was used to measure global cognitive functioning. Depression was measured with the depression part of the Problem Behaviours Assessment short version[26], where depressive feelings are scored by severity and frequency (score range 0-16). The neurological assessment was performed at both visits by clinicians specialized in HD, blinded for genetic status.

Sustained Attention to Response Test

The SART was administered during both visits under the same conditions. Subjects were seated in a comfortable chair one meter from a computer screen, with a

computer keyboard placed in easy access of the dominant hand. Numbers from 1 to 9 were each shown 25 times on a computer screen. Subjects were asked to respond to every number by pressing a spacebar ('Go' trials), except when the number 3 was shown ('No-go' trials). In the case of a No-go trial subjects were instructed to withhold their response. Accuracy and speed were instructed to be equally important. Before the test subjects were allowed to practice with 25 random trials. The numbers were shown for 250 milliseconds followed by a blank screen for 900 milliseconds[14]. Reaction time (RT) was recorded whenever the spacebar was pressed. To ensure accurate measurement of RT a cathode ray screen was used together with a purpose built hardware device that allowed precise measurement of the build-up time of the screen information and hence of RT in relation to the visual stimulus[18].
Outcome measures for the SART were reaction time (RT) and number of errors. 'Overall RT' refers to mean RT over all trials performed. Errors are divided into total number of errors, and errors on Go and No-go trials. For error processing analyses the mean RT of the trials directly preceding and directly following both correct and incorrect No-go trials were used ('3' is the No-go item in the SART). A delta score was also computed, which comprised the difference between the mean RT on the trials directly preceding and directly following both correct and incorrect (i.e. an incorrect response to a three) No-go trials.

ERP recording and analysis

Twenty-one Ag/AgCl electrodes were placed according to the 10/20 convention. ECG, respiration and horizontal eye movement leads were also recorded. The EEG was band-pass filtered from 0.16-70 Hz before display and analysis. Sample frequency was 200 Hz and A-D precision 12 bits. For the P300 analysis we used the midline sites Fz (frontal), Cz (central) and Pz (parietal) with linked mastoids as reference. The computer controlling the SART paradigm wrote synchronization signals to the EEG machine, allowing averaging to take place offline after controlling for signal quality. Data were averaged over epochs of 1200 ms, starting 200 ms before stimulus onset. Individual trials with eye blink artefacts or suspected muscle artefacts were excluded from P300 analysis. The P300 component was defined as the maximum positivity between 350 and 650 ms. ERP analysis, including peak detection, was performed automatically using an in-house developed program written in MATLAB (The MathWorks, Natick, USA). Peak amplitudes were measured relative to a 200 ms baseline before stimulus onset. P300 outcome measures consisted of amplitude and latency data. The mean amplitudes and latencies for all trials, all Go trials and all No-go trials were calculated[18].

Statistical analysis

Data analysis was done using IBM SPSS statistics for Windows, version 20.0. Demographic variables were compared between groups using ANOVA (continuous variables) and Pearson's χ^2 (categorical variables). Classification of the groups at baseline was used for all analyses. ANCOVA was done for cross-sectional SART and P300 analyses, where separate analyses were performed for baseline and follow-up visits. For SART error scores, the age and mean RT at time of visit were used as covariates. Age was chosen because of the known effect of aging on neuropsychological testing. With the inclusion of RT as covariate we assume to test more pure cognitive performance while controlling for possible differences in RT. For the RT, P300 and error processing analyses, age at time of visit was selected as covariate. Again, age has been proven to have an altering effect on both RT and P300 characteristics. For longitudinal analyses of between group effects, delta scores (follow-up visit score-baseline visit score) were calculated and analyses of covariance were performed on these scores. Age at baseline was used as covariate, except for the analyses of SART error scores where age and mean RT at baseline were selected. Significant main results were further investigated using Bonferroni post-hoc tests. Within subjects effects were investigated using paired samples t-tests. Effect sizes are reported as partial eta squared values. The level of statistical significance was set at $p \leq 0.05$. For both cross-sectional as longitudinal analyses Bonferroni correction was applied to correct for multiple testing.

RESULTS

Demographic data

Demographic and clinical data of baseline and follow-up visits are shown in Table 1. The groups were similar in terms of age, gender, education, and total functional, depression and MMSE scores on both visits. MHD subjects had a higher disease burden than PMHD subjects ($F(1, 12) = 12.41$, $p = 0.004$). The TMS of the MHD group was higher than the TMS of the PMHD ($F(2, 23) = 8.89$, $p = 0.002$) and control group (visit 1: $F(2, 23) = 8.89$, $p = 0.003$, and visit 2: $F(2, 23) = 8.89$, $p < 0.001$) on both visits.

Cross-sectional data

Cross-sectional data of the SART and P300 are shown in Table 2. MHD subjects made more total ($F(2, 21) = 4.07$, $p = 0.03$, $\eta_p^2 = 0.280$) and No-go errors ($F(2, 21) = 5.18$, $p = 0.02$, $\eta_p^2 = 0.330$) on both visit 1, and visit 2 ($F(2, 21) = 7.30$, $p = 0.004$, $\eta_p^2 = 0.410$, and $F(2, 21) = 8.80$, $p = 0.002$, $\eta_p^2 = 0.456$, respectively) compared to PMHD subjects and controls. Additionally, the MHD group reacted slower on visit 2 ($F(2, 22) = 9.51$, $p = 0.001$, $\eta_p^2 = 0.464$) compared to PMHD

subjects and controls.
Concerning the P300 characteristics MHD subjects showed a longer overall (visit 1 $F(2, 22) = 3.68$, $p = 0.04$, $\eta_p^2 = 0.250$), Go (visit 1 $F(2, 22) = 3.53$, $p = 0.047$, $\eta_p^2 = 0.243$ and visit 2 $F(2, 22) = 4.14$, p=0.03, $\eta_p^2 = 0.273$) and No-go (visit 1 $F(2, 22) = 4.64$, $p = 0.02$, $\eta_p^2 = 0.297$) latency than PMHD and control subjects. Also, the MHD group demonstrated a lower No-go amplitude than the control group on visit 1 ($F(2, 22) = 3.69$, $p = 0.04$, $\eta_p^2 = 0.251$).

Table 1: Descriptive statistics at baseline and follow-up visits

Characteristic		Premanifest HD N=9	Manifest HD N=5	Controls N=12
Age (years)	baseline	40.3 (10.0)	45.4 (10.7)	48.2 (9.7)
	follow-up	43.4 (9.7)	48.4 (10.7)	51.3 (9.7)
Gender, m/f[a]	baseline	3/6	2/3	5/7
Education (years)	baseline	12.3 (2.6)	14.4 (2.9)	11.9 (2.7)
CAG repeat length	baseline	41.3 (1.5)	44.4 (3.1)	20.0 (2.9)
Disease burden	baseline	232.2 (73.3)	382.5 (82.5)	
	follow-up	250.7 (75.8)	409.2 (90.7)	
Total motor score	baseline	1.6 (2.5)	6.4 (1.3)	2.0 (2.2)
(range 0-124)	follow-up	2.2 (1.5)	14.8 (7.7)	3.0 (3.4)
Total functional capacity	baseline	12.2 (1.1)	12.0 (1.4)	13.0 (0)
(range 0-13)	follow-up	11.8 (1.6)	12.0 (1.2)	12.8 (0.6)
PBA-s depression score	baseline	2.8 (2.9)	2.2 (3.3)	3.0 (3.5)
(range 0-16)	follow-up	1.0 (2.1)	2.0 (2.0)	1.1 (1.6)
Score MMSE	baseline	28.8 (0.8)	28.4 (0.9)	29.0 (1.0)
(range 0-30)	follow-up	28.8 (1.2)	28.6 (1.5)	29.4 (0.7)

Note. Data is presented as mean (SD), [a] is total number.

Longitudinal data

No between-group effects were found longitudinally for SART and P300 data. Concerning within-subjects differences, paired samples t-tests showed a significant mean RT increase over time on the SART for MHD participants ($t(4)$ = -9,56, p = 0.01, η_p^2 = 0.938).
A prolongation of the No-go P300 latency was found for controls ($t(11)$ = -3.56, p = 0.004, η_p^2 = 0.494) and of the Go latency for MHD ($t(4)$ = -2.82, p = 0.048, η_p^2 = 0.570). No significant changes were observed concerning P300 amplitude.

SART error processing analyses cross-sectional data

Data for the error processing analysis are shown in Table 3. Cross-sectionally, MHD subjects reacted slower on the trial directly following both correctly ($F(2, 22)$ = 3.75, p = 0.04, η_p^2 = 0.254) and incorrectly ($F(2, 21)$ = 5.49, p = 0.01, η_p^2 = 0.343) withheld responses to No-go trials (appearance of the number '3') compared to controls at visit 1. MHD subjects were also slower in reacting to the trial just preceding a correct No-go ($F(2, 22)$ = 6.03, p = 0.007, η_p^2 = 0.364) and following both correct ($F(2, 22)$, $p < 0.001$, η_p^2 = 0.544) and incorrect ($F(2, 22)$, $p < 0.001$, η_p^2 = 0.542) No-go trials, all compared to both controls and PMHD participants at visit 2.

SART error processing analyses longitudinal data

ANCOVA on delta scores revealed between group differences for trials preceding a correct No-go trial. RT in all groups became longer over time, but MHD subjects became significantly more so than the other groups ($F(2, 22)$ = 6.22, p = 0.007, η_p^2 = 0.361). Regarding within-subject effects paired samples t-tests showed that both MHD ($t(4)$ = -5.15, p = 0.007, η_p^2 = 0.815) and PMHD ($t(8)$ = -2.68, p = 0.03, η_p^2 = 0.418) participants became slower over time on trials directly preceding correct No-go trials.

Table 2: SART and P300 data: cross-sectional and longitudinal within-subjects and between-group analyses

SART	Group PMHD (N=9) MHD (N=5) Controls N=12	Baseline	Follow-up	Cross-sect baseline p-value	Cross-sect follow-up p-value	Longit[a] within-subjects p-value	Longit[b] between-group p-value
	PMHD	7.9 (4)	6.7 (3)			0.171	
Total error	MHD	12.0 (8)	12.4 (4)	<**0.05**	<**0.01**	0.889	0.267
	Controls	8.2 (5)	9.3 (3)			0.362	
	PMHD	6.9 (3)	6.4 (3)			0.559	
No-go error	MHD	10.8 (7)	8.8 (4)	<**0.05**	<**0.01**	0.417	0.140
	Controls	7.1 (4)	8.3 (3)			0.234	
	PMHD	1.0 (2)	0.2 (0)			0.211	
Go error	MHD	1.2 (2)	3.6 (4)	0.596	0.421	0.170	0.587
	Controls	1.1 (1)	0.9 (1)			0.732	
	PMHD	361.4 (32)	374.9 (33)			0.098	
Mean RT	MHD	422.9 (81)	481.9 (84)	0.055	<**0.01**	<**0.01**	0.174
	Controls	371.2 (29)	379.9 (39)			0.435	

Table continued on next page.

Table 2: **(Continued)** SART and P300 data: cross-sectional and longitudinal within-subjects and between-group analyses

P300	Group PMHD (N=9) MHD (N=5) Controls N=12	Baseline	Follow-up	Cross-sect baseline p-value	Cross-sect follow-up p-value	Longit[a] within-subjects p-value	Longit[b] between-group p-value
	PMHD	380 (18)	394 (36)			0.138	
Latency	MHD	435 (46)	451 (58)	**<0.05**	0.089	0.313	0.760
	Controls	406 (39)	413 (39)			0.407	
	PMHD	391 (34)	420 (47)			0.080	
Lat No-go	MHD	449 (62)	474 (45)	**<0.05**	0.081	0.453	0.850
	Controls	408 (22)	432 (33)			**<0.001**	
	PMHD	375 (21)	396 (36)			0.119	0.204
Latency Go	MHD	430 (45)	454 (53)	**<0.05**	**<0.05**	**<0.05**	
	Controls	409 (41)	406 (30)			0.646	
	PMHD	10.2 (5)	9.6 (4)			0.597	0.674
Amplitude	MHD	7.8 (3)	8.2 (2)	0.427	0.736	0.630	
	Controls	9.6 (3)	8.9 (3)			0.222	
	PMHD	17.3 (6)	16.5 (5)			0.534	
Amp No-go	MHD	10.9 (3)	14.1 (6)	**<0.05**	0.406	0.223	0.111
	Controls	17.8 (4)	17.6 (5)			0.742	
	PMHD	9.6 (5)	9.1 (5)			0.628	
Amplitude Go	MHD	7.6 (3)	7.8 (2)	0.449	0.698	0.769	0.767
	Controls	8.3 (3)	7.9 (3)			0.221	

Note. Data is presented as mean (SD). [a]paired samples t-tests; [b]ANCOVA on delta-scores. RT = reaction time in milliseconds. Amplitude is in microvolts (μV). Latency is in milliseconds, MHD=manifest HD, PMHD=premanifest HD.

Table 3: SART error analysis data: cross-sectional and longitudinal within-subjects and between-group analyses

	Group PMHD (N=9) MHD (N=5) Controls N=12	Baseline	Follow-up	Cross-sect baseline p-value	Cross-sect follow-up p-value	Longit[a] within-subjects p-value	Longit[b] between-group p-value
Correct 3							
RT	PMHD	336 (21)	392 (43)			<**0.05**	
before	MHD	426 (92)	535 (128)	0.070	<**0.01**	<**0.01**	<**0.01**
	Controls	409 (43)	416 (67)			0.760	
RT	PMHD	314 (57)	349 (37)			0.054	
after	MHD	381 (76)	421 (70)	<**0.05**	<**0.001**	0.223	0.099
	Controls	317 (18)	310 (23)			0.442	
Incorrect 3							
RT	PMHD	338 (45)	350 (48)			0.391	
before	MHD	350 (39)	444 (194)	0.777	0.185	0.278	0.115
	Controls	349 (35)	364 (53)			0.625	
RT	PMHD	414 (85)	360 (36)			0.092	
after	MHD	476 (104)	529 (108)	<**0.05**	<**0.001**	0.435	0.118
	Controls	338 (54)	363 (59)			0.414	

Note. Data are mean (SD). Reaction time are milliseconds. [a]paired samples t-tests; [b]ANCOVA on delta-scores, MHD=manifest HD, PMHD=premanifest HD, RT = Reaction Time.

DISCUSSION

In this pilot-study we present preliminary data on longitudinal SART and simultaneous P300 assessment in HD. To our knowledge we are the first to perform a longitudinal ERP study in premanifest HD. We found that over a course of three years MHD subjects showed an increase in RT on the SART, and exhibited a prolongation of the P300 latency on specific trials of the SART. PMHD subjects only showed specific increase in reaction time just before having prevented a possible error on the SART.

In the MHD group we replicated the findings of the cross-sectional study by Hart et al.[18] on the SART and P300 in HD where MHD subjects make more errors on the SART than both other groups, and took longer to react to the trials (follow-up visit). The increase in reaction time is not surprising, and is likely to reflect motor slowing. This conclusion is strengthened by only specific, and not overall, RT increase in the PMHD subjects. In the earlier study the authors hypothesized that the observed slowing could reflect a speed-accuracy trade-off, a (conscious or unconscious) strategy applied by MHD participants to maintain task requirements[27]. The increase in RT seen in the current MHD cohort does however not prevent these subjects from making more mistakes than the other two groups. So, there is no task-related benefit from the motor slowing. One explanation for this absence of benefit could be that the employment of the speed-accuracy trade-off has reached a maximum. If this level is reached the impairment can no longer be compensated and task-related benefit is absent.
The MHD group also showed the most pronounced RT increase over time, which was expected in view of the neurodegenerative nature of HD. Neurodegeneration is also reflected in the neurophysiologic data, as demonstrated by the cross-sectionally longer P300 latencies compared to the other groups, and the latency prolongation over time on Go trials. The P300 latency has been linked to stimulus evaluation time, or generalized, cognitive processing speed[28], so a lengthened latency in the MHD group could reflect reduced processing speed. Deficits in processing speed have also been demonstrated by other authors using other paradigms[29 30].

Cross-sectionally, premanifest subjects perform equally to control subjects, evident by the lack of cross-sectional results. Interestingly, in the PMHD group we did find specific slowing over time. During follow-up this group became slower in reacting to trials directly preceding correct No-go trials (i.e. correctly withholding the response to the appearance of a '3'). This slowing was also seen in the MHD group, but only MHD subjects produced more errors than controls. The exact significance of such specific deterioration is difficult to explain, but as the PMHD subjects make the same number of errors as controls and increase in RT where controls do not, this could mean that it takes more attentional demands for PMHD subjects to maintain task performance. As PMHD subjects can keep up with the

demands of the SART it could mean that the RT increase is the result of some kind of compensatory mechanism. That it reflects pure motor slowing is less likely as in this case we would have expected increased RT on more variables.
A candidate compensatory mechanism here could be speed-accuracy trade-off, a strategy that was used by MHD subjects in the cross-sectional study[18]. That growing attentional demands could translate into increased RT is well described in speed-accuracy trade-off literature[27]. Additionally, the controls did not slow over time on these specific trials, and produced a similar amount of errors as the PMHD subjects. This strengthens our hypothesis that some kind of compensation is utilized by the latter group. This proof of early compensation by means of speed-accuracy trade-off in PMHD complements our earlier hypothesis that in the current MHD cohort the maximum level of compensation (by means of speed-accuracy trade-off) is reached and no more task-related benefits are observed.
That compensatory mechanisms are at work in PMHD has been suggested before[31]. In another basal ganglia disorder, Parkinsons disease (PD), compensatory mechanisms responsible for delaying overt symptom onset have long been accepted[32]. Here, even several compensatory networks have been identified postponing the final appearance of parkinsonism[33]. Looking at our overall raw data we also see that for SART errors and mean RT scores the premanifest subjects perform better not only than the MHD, but also than the control subjects. This could reflect overall compensation to perform at pre-disease level.

The significant post-error slowing that was found in the previous cross-sectional study was not replicated in the present study. An explanation for this could be that the manifest group, consisting of five subjects, was too small to make this difference visible. Also, individual differences in such a small sample could have large effects. This is evident in the differences in RT patterns surrounding incorrect responses to a No-go trial, where at baseline some post-error slowing was visible (albeit not statistically significant) for MHD and PMHD, while it was absent at follow-up.

As our preliminary data derived from small pilot groups our conclusions should be considered with caution. Generalization of our results is limited as, due to the sample sizes, statistical power is low and the impact of individual fluctuations in scores more influential.
The combination of cognitive testing (SART) with simultaneous P300 registration is a strength of this study, in the way that the P300 is independent of motor slowing whereby conclusions about cognitive functioning can be made more easily. Following the specific result in the PMHD group we recommend replication of this pilot-study with larger numbers of participants in order to be better able to understand the transition from premanifest to manifest HD.

In conclusion, this pilot-study partly replicated the findings from the cross-sectional

study by Hart and colleagues[18] that MHD subjects perform worse than both PMHD and control subjects on tests of attentional control. MHD subjects are slower and make more mistakes on the SART, and show longer P300 latencies. Longitudinal change in attentional control was observed for specific trials in the PMHD subjects, which could be suggestive of compensatory mechanisms in this phase of HD.

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