



Task-switching abilities in pre-manifest Huntington's disease subjects

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ABSTRACT

Introduction: Huntington's Disease (HD) cognitive dysfunction occurs before unequivocal motor signs become apparent. The predominant early cognitive abnormal domains may include deficits in psychomotor speed, negative emotion recognition and executive functioning. Our study is aimed to investigate the executive control of cognition in pre-manifest (pre) HD subjects, by means of a task-switching protocol.

Methods: We recruited 30 pre-HD subjects and 18 age-, sex- and education-matched Healthy Controls (HC). Subjects were assigned to two experimental groups: 15 pre-HD1 with a Total Motor Score (TMS) ≤ 4 (far from onset) and 15 pre-HD2 with a $5 \leq \text{TMS} \leq 9$ (near to onset and Diagnostic Confidence Level (DCL) still < 4). Two different tasks were performed in rapid and random succession, so that the task was either changed from one trial to the next one (switch trials) or repeated (repetition trials). Switch trials are usually slower than repetitions, causing a so-called Switch Cost (SC).

Results: Pre-HD subjects had worse performance than HC in the switch and repetition trials, as indicated by increased SC and reaction times. In particular, pre-HD2 showed impaired switching abilities with reaction times slower than pre-HD1 and HC.

Conclusions: Our study highlighted a task-switching impairment since HD was still at a pre-manifest stage. Such abnormalities worsen when pre-HD subjects start to show subtle motor manifestations, still nonspecific and insufficient to define the clinical diagnosis of HD (DCL < 4). Considering that such abilities have obvious implications for activities of daily living, early cognitive rehabilitation programs addressing such deficits might be useful in the premanifest stage of the disease.

1. Introduction

Huntington's disease (HD) is a progressive neurodegenerative disorder characterized by motor symptoms (i.e. involuntary movements, incoordination), cognitive impairment and psychiatric behavior [1].

Motor manifestations are related to progressive neurodysfunction and neurodegeneration in basal ganglia, particularly in the striatum and its spiny projections toward the globus pallidus and substantia nigra [2]. However, other brain abnormalities are observed: white matter atrophy is observed from early disease stages [3,4], followed by marked brain atrophy in the thalamus, hypothalamus, and frontal regions [5,6].

These cerebral modifications lead to a wide range of cognitive impairments in the premanifest (i.e., asymptomatic persons carrying the HD gene) and the manifest stage (i.e., symptomatic individuals presenting motor and/or cognitive and/or psychiatric symptoms) [1,2].

Cognitive dysfunction begins many years before motor onset; the

primary neuropsychological impairment in the premanifest stage of the disease can involve difficulties in emotion recognition and emotional awareness [7–9] as well as in executive functioning [10,11], whereas manifest subjects exhibit a more general and widespread cognitive deterioration including memory, attention, language, and disorientation until overt dementia in the late stage of the disease.

However, cognitive evidence still remains inconsistent in pre-manifest HD subjects, particularly regarding executive impairments [12,13], because such abilities include numerous sub-components, each with different characteristics and neural substrates.

Executive functions (EF) are important abilities needed for complex goal-directed behavior and adaptation to environmental changes [14]. Executive skills include different sub-functions, for example inhibition, attentional shifting, behavioral flexibility, planning and problem solving. It is widely accepted that EF are critical to everyday functioning in life: people who have difficulty inhibiting themselves, planning, problem solving and/or being flexible, will also show major deficits in

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social, academic and vocational functioning.

The task-switching paradigm has proven to be very useful in the study of some components of executive functioning [15] and has been widely used to investigate the executive control of cognition (for a review see Refs. [15,16]). Neuroimaging studies have demonstrated that the task-switching performance recruits various prefrontal cortex (PFC) regions [17]. It has been also shown that this task is very sensitive to sleep manipulation [18] as well as to some neurodegenerative diseases [19,20].

In this type of procedure, two different tasks are performed in rapid succession and according to a random sequence of task presentation, so that the to-be executed task can change from one trial to the next (“switch” trial), or can be repeated (“repetition” trial). Task-switches are usually slower and less accurate than task repetitions, and this difference is often referred to as the “task-switch cost” (SC). This cost is seen as the reflection of the time needed for the executive control processes to reconfigure the cognitive system for the execution of a new task [21]. Thus, the SC can be reasonably considered the operational measure of executive control.

The task-switching protocol has been largely used in Parkinson's Disease (PD) and in Multiple Sclerosis (MS), showing its usefulness and sensitiveness in assessing different executive sub-processes in early phases of the disease [20,22].

On the contrary, only one study tried to assess switching abilities in HD [23]. In this study, the authors provided evidence for a switching deficit in manifest HD patients, with higher reaction times mainly for switch trials with respect to repetition trials, particularly when the preparation time interval was short. The authors concluded that basal ganglia could have a relevant role in executive dysfunction, influencing response processes underpinning executive functioning. The main limitation of that study relied on the fact that only the manifest stage was taken into consideration, without investigating the premanifest stage of HD.

In our study, we aimed to assess whether (and how) primary executive impairment may be detected in the premanifest stage of HD, by means of a task-switching protocol based on its well-known sensitiveness to evaluate different sub-processes of executive functioning. Moreover, task-switching skills are associated with fronto-striatal brain functioning, a circuitry that can be impaired early in HD [6,24].

2. Materials and methods

2.1. Participants

We recruited 30 premanifest HD (pre-HD) subjects, from July 2017 to December 2017, belonging to two groups: 15 participants with Total Motor Score (TMS) ≤ 4 (premanifest, pre-HD1) and 15 participants with $5 \leq \text{TMS} \leq 9$ (prodromal, pre-HD2), compared to 18 healthy controls (HC) matched to age, gender and education. All subjects had an CAG/Age Product (CAP) [25] score below 400 [26]. HD was

genetically confirmed in all cases (all with CAG expansion ≥ 40). Demographic, clinical and genetic characteristics are reported in Table 1.

The pre-HD groups underwent a neurological examination and were assessed using the Unified Huntington's Disease Rating Scale (UHDRS) [27]. All pre-HD subjects were free of medication at time of the assessment. We excluded HD subjects with any known neurological condition (other than HD), medical condition that might influence cognition (i.e. deafness, visual impairment or blindness), a history of a developmental disorder (e.g. attention-deficit hyperactivity disorder (ADHD), learning disability), a history of substance or alcohol dependence or current abuse and a history of or a current psychotic disorder. The participants were recruited at LIRH Foundation and C.S.S. Mendel Institute in Rome. This observational study was designed in accordance with the ethical principles of the Declaration of Helsinki and was approved by the local ethical committee: as a consequence, all participants signed an informed consent.

2.2. Clinical and neuropsychological assessment

Both HD subjects and healthy controls underwent a brief preliminary cognitive evaluation, to assess general cognitive performance, which included the Symbol Digit Modalities Test (SDMT), the Trail Making Test part A and B (TMT A – B), the Stroop test (color naming, word reading, interference), and the Verbal Fluency test (both semantic and phonemic versions). Cognitive tests were administered in a standardized manner, in accordance with ENROLL-HD guidelines (www.enroll-hd.org) [27].

Moreover, we evaluated behavioral symptoms by means of the Symptoms Checklist-90-R (SCL-90R) [28], a relatively brief self-report questionnaire designed to evaluate a broad range of psychological problems and symptoms of psychopathology. It includes many dimensions, for example: depression, anxiety, hostility/irritability, obsessive-compulsive symptoms, paranoid ideation, psychoticism. Finally, the 12-item Short-Form Health Survey (SF-12) was used to assess general health status.

2.3. Task-switching

Participants were tested individually in a well-lit, sound-proof room. They were seated in front of a 15-inch computer monitor, at a distance of 50 cm, and at the beginning of each session, task instructions were both displayed on the screen and explained verbally to each of them, emphasizing the need for both accuracy (avoiding errors) and speed (minimize reaction times).

Participants performed two tasks in rapid sequence, in randomized order; in these tasks, a cue (the “square” or “diamond” respectively) in each trial indicated the task to perform on the subsequent target stimulus that appeared inside the cue. The two tasks consisted of judging if a digit stimulus was odd or even (task A), or if it was greater or smaller than 5 (task B). Participants used their left and right index

Table 1
Demographic and clinical characteristics (mean $\pm$ standard deviation) of the study sample.

	Premanifest HD (pre-HD1)	Prodromal HD (pre-HD2)	Healthy Controls (HC)	p
Number	15	15	18	n.s
Gender (F-M)	5 F–10 M	10 F–5 M	8 F–10 M	n.s
Age (years $\pm$ SD)	32.38 $\pm$ 7.62	36.26 $\pm$ 10.78	31.67 $\pm$ 13.09	n.s
Education	14.33 $\pm$ 4.22	12.4 $\pm$ 3.33	14.11 $\pm$ 1.68	n.s
CAG Expansion	43.07 $\pm$ 2.25	42.87 $\pm$ 1.96		n.s
CAP	236.51 $\pm$ 60.32	262.77 $\pm$ 84.68		n.s
TMS	3.33 $\pm$ 0.9	6.87 $\pm$ 1.6		p < .0001
TFC	13	13		n.s
FA	25	25		n.s
IS	100	100		n.s

HD: Huntington Disease; TMS: Total Motor Score; TFC: Total Functional Capacity; FA: Functional Assessment; IS: Independent Scale; Disease burden score: age * (CAG length - 35.5); n.s: not significant.

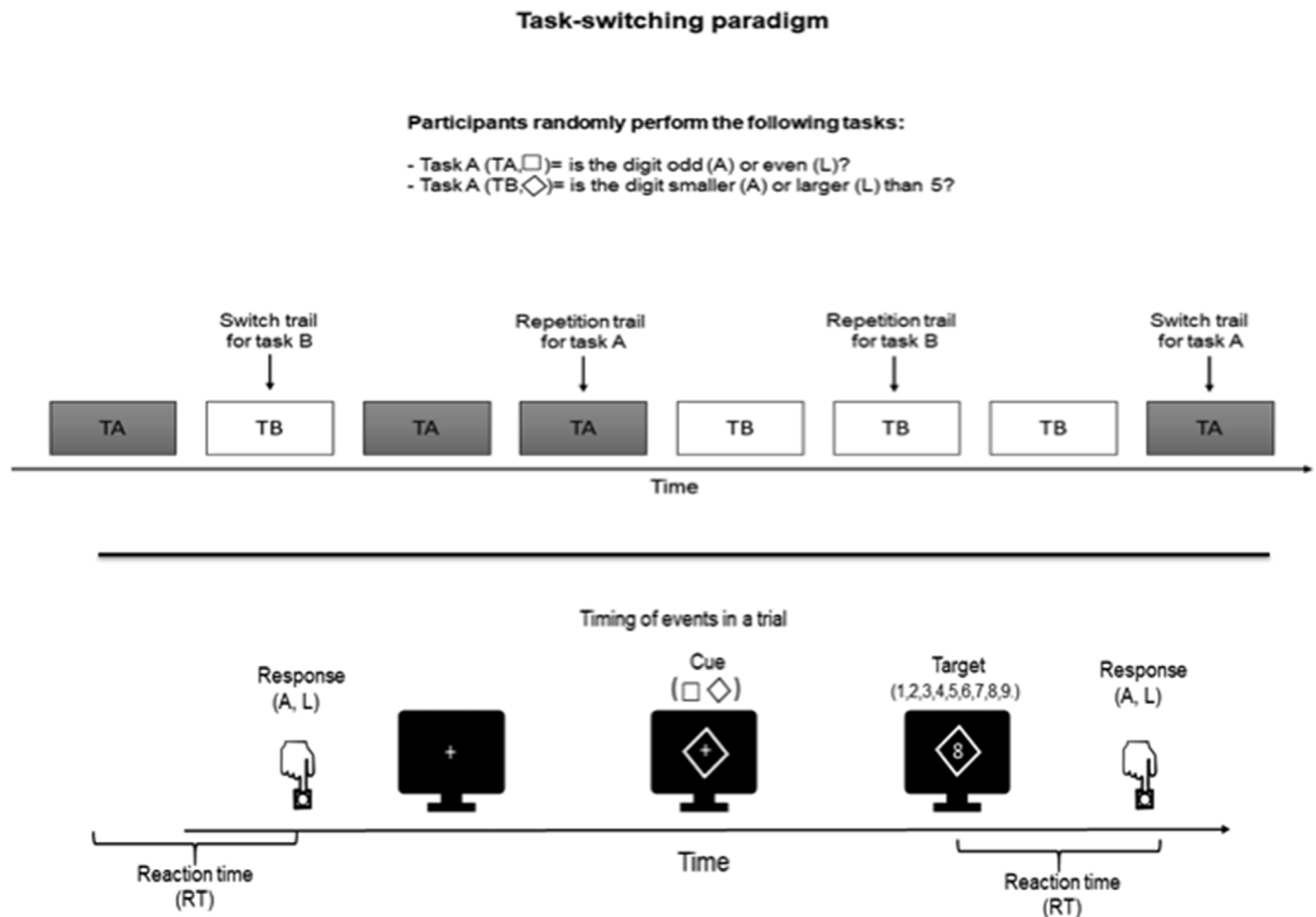


Fig. 1. Task-switching paradigm. On the upper panel, an example of a sequence of repetition and switch trials is reported. On the lower panel, the timing of the events within a single trial is specified. Target stimuli consisted of bold white digits from 1 to 9 (excluding 5), subtending approximately $3^\circ \times 5^\circ$ of visual angle. Task cues stimuli consisted of outlined white squares or diamonds, indicating the A (even–odd) and B (smaller–larger-than-5) tasks, respectively; they subtended approximately $7^\circ \times 7^\circ$ of visual angle.

fingers to respond: odd digits and digits smaller than 5 were mapped onto the left index finger response, whereas even digits and digits larger than 5 were mapped onto the right index finger response. The same two response keys on the computer keyboard ('A' for left and 'L' for right index finger) were used for both tasks. Stimuli presentation and response recordings were managed by means of custom software (Superlab, version 4.0.2 for Windows). Each participant initially performed a practice session (1 block of 80 trials) followed by an experimental session consisting of 320 trials, arranged in 4 blocks of 80 trials each.

On each trial a cue was presented for 1000 ms and then it was followed by a target stimulus which remained on the monitor until the participant's response. If the participant made an error, an auditory feedback error was given. A schematic illustration of the sequence of events in the present task-switching paradigm is reported in Fig. 1.

2.4. Statistical analyses

Statistical comparisons between pre-HD1 (TMS ≤ 4), and pre-HD2 groups ($5 \leq \text{TMS} \leq 9$) on functional status (TFC, FA, and IS), were carried out by means of the Student's t-test.

Regarding clinical and neuropsychological scales and task-switching protocol, all dependent variables were submitted to one-way ANOVA directly comparing performance of different Groups (pre-HD1, pre-HD2, controls).

With regards to the neuropsychological evaluation, in the verbal

fluency test (semantic and phonemic) we considered the median of correct responses, intrusion and perseveration. Regarding the Stroop Test (word reading, color naming and interference) and SDMT we considered the median of correct responses. Finally, in TMT (version A and B), we measured median reaction times to complete the test.

With regards to task-switching protocol, median reaction times (in ms; median RT) to both repetition and switch trials, switch costs (SCs), and angular transformations of the proportion of errors were taken into consideration as dependent variables. SCs were computed as the difference between median switch RT and median repetition RT. For each subject, proportions of errors were computed by including both incorrect and missing responses. Before statistical analysis, this variable was submitted to an angular transformation, $y = \arcsin[\sqrt{p}]$, where $\sqrt{p}$ is the square root of the proportion. Alpha level was fixed to ≤ 0.05 , and in case of significant main effects, post-hoc comparisons (Fisher's least significant difference test, LSD) were carried out.

3. Results

3.1. Functional and motor status

Student's t-test revealed no statistically significant differences between pre-HD1 and pre-HD2 groups, in any of the considered variables related to the functional status of the patients (TFC, FA, and IS). As expected, significant difference emerged in TMS ($p < .0001$) between pre-HD1 (3.33 ± 0.9) and pre-HD2 (6.87 ± 1.6). Table 1 shows

demographic and clinical characteristics of the study sample.

3.2. Clinical and neuropsychological assessment

SCL-90R. No statistically significant differences between groups were observed in any of the SCL-90R variables.

SF-12. No statistically significant differences between groups were observed in any of the SF-12 variables.

Verbal Fluency test - Semantic version. In the semantic version, a significant Group effect ($F_{2,45} = 3.81$; $p = .03$; $\eta^2 = 0.14$) was observed, showing a higher number of intrusions in the pre-HD2 group (0.40 ± 0.73) compared to pre-HD1 (0.07 ± 0.25) and controls (0 ± 0). *Post-hoc* comparisons revealed a significant difference between pre-HD1 and pre-HD2 ($p = .04$), and between pre-HD2 and controls ($p = .01$). Any other effect was found either in the number of correct responses, and perseverations.

Verbal Fluency test - Phonemic version. No effects have been reported in any of the dependent variables of the test.

Stroop test. The one-way ANOVA showed a significant Group effect on number of correct responses at Stroop Color ($F_{2,45} = 7.73$; $p = .001$; $\eta^2 = 0.25$) and Stroop Interference ($F_{2,45} = 17.81$; $p < .0001$; $\eta^2 = 0.44$) components, indicating a lower accuracy in pre-HD2 than in pre-HD1 and control group, both color (pre-HD1 = 78.6 ± 14.63 vs pre-HD2 = 73.8 ± 14.14 vs HC = 91.33 ± 11.37) and interference (pre-HD1 = 46.87 ± 11.11 vs pre-HD2 = 41.87 ± 10.51 vs HC = 65.89 ± 14.43) components. Here, *post-hoc* comparisons indicated a significant difference both between pre-HD1 and controls ($p = .009$), and between pre-HD2 and controls ($p < .0001$) in number of correct responses at Stroop color naming, and a significant difference both between pre-HD1 and controls ($p < .0001$), and pre-HD2 and controls ($p < .0001$) in number of correct responses at Stroop Interference.

Trial Making Test. One-way ANOVA showed a significant Group effect ($F_{2,45} = 3.51$; $p = .03$; $\eta^2 = 0.13$) relative to time to complete the TMT A task, evidencing higher values in pre-HD2 (33.40 ± 12.45) than in pre-HD1 (24.87 ± 5.7) and controls (25.78 ± 9.93). *Post-hoc* comparisons indicated a significant difference both between pre-HD1 and pre-HD2 groups ($p = .02$), and pre-HD2 and controls ($p = .03$).

No statistically significant differences between the groups were seen for TMT B.

Symbol Digit Modalities Test (SDMT) The one-way ANOVA revealed a significant Group effect ($F_{2,45} = 4.56$; $p = .01$; $\eta^2 = 0.16$), indicating a lower number of correct responses in pre-HD2 (49.53 ± 8.83) than pre-HD1 (54.8 ± 9.93) and control (64.11 ± 19.5) groups. *Post-hoc* comparisons revealed a significant difference only between pre-HD2 and controls ($p = .005$).

Table 2 shows neuropsychological scores.

3.3. Task switching protocol

Switch costs (SC). One-way ANOVA showed a significant Group effect ($F_{2,45} = 4.81$; $p = .01$; $\eta^2 = 0.17$) evidencing a higher SC in pre-HD2 (360.98 ± 7.98) than in pre-HD1 (192.84 ± 10.32) and control (76.56 ± 7.98) groups. *Post-hoc* comparisons revealed a significant difference only between pre-HD2 and controls ($p = .003$) (see Fig. 2).

Reaction times (RT)-Repetition trials. One-way ANOVA revealed a significant Group effect ($F_{2,45} = 8.69$; $p = .001$; $\eta^2 = 0.28$) indicating a higher reaction time at Repetition trials in pre-HD2 (920.8 ± 14.90) than pre-HD1 (895.5 ± 14.13) and control (683.97 ± 10.74) groups. *Post-hoc* comparisons revealed a significant difference both between pre-HD1 and controls ($p = .002$) and pre-HD2 and controls ($p = .001$) (see Fig. 3a).

Reaction times (RT)-Switch trials. Also, a significant Group effect ($F_{2,45} = 11.66$; $p < .0001$; $\eta^2 = 0.34$) was observed at Switch trials indicating a higher reaction times in pre-HD2 (1201.133 ± 19.99) than pre-HD1 (1099.7 ± 15.76) and controls (755.61 ± 12.63). *Post-*

Table 2
Neuropsychological scores in different groups of the subjects.

	Healthy Controls (HC)	Pre-manifest HD (pre-HD1)	Prodromal HD (pre-HD2)	P	Post-Hoc	P (HC vs preHD1)	P (HC vs preHD2)	P (preHD1 vs preHD2)
VERBAL FLUENCY-SEMANTIC (correct response)	22.28 ± 4.11	21.6 ± 4.3	19.8 ± 5.68	NS	NS	NS	NS	NS
VERBAL FLUENCY-SEMANTIC (intrusion)	0	0.07 ± 0.25	0.4 ± 0.73	0.03	NS	NS	0.01	0.04
VERBAL FLUENCY-SEMANTIC (perseveration)	0.17 ± 0.51	0	0	NS	NS	NS	NS	NS
VERBAL FLUENCY-SEMANTIC (correct response)	46.78 ± 10.36	41.27 ± 12.02	41.73 ± 12.51	NS	NS	NS	NS	NS
VERBAL FLUENCY-PHONEMIC (intrusion)	0.22 ± 0.64	0.07 ± 0.25	0.13 ± 0.35	NS	NS	NS	NS	NS
VERBAL FLUENCY-PHONEMIC (perseveration)	0.83 ± 1.15	0.93 ± 1.53	0.53 ± 0.91	NS	NS	NS	NS	NS
STROOP TEST - WORD (correct response)	106.5 ± 14.55	105.8 ± 18.47	97.53 ± 18.58	NS	NS	NS	NS	NS
STROOP TEST - COLOR (correct response)	91.33 ± 11.37	78.6 ± 14.63	73.8 ± 14.14	0.001	0.009	0.0001	0.0001	NS
STROOP TEST - INTERFERENCE (correct response)	65.89 ± 14.43	46.87 ± 11.11	41.87 ± 10.51	0.0001	0.0001	0.0001	0.0001	NS
TMT - A (time)	25.78 ± 9.93	24.87 ± 5.7	33.4 ± 12.45	0.03	NS	NS	0.03	0.02
TMT - B (time)	56.28 ± 17.28	48.53 ± 18.2	57 ± 15.72	NS	NS	NS	NS	NS
SDMT (correct response)	64.11 ± 19.5	54.8 ± 9.93	49.53 ± 8.83	0.01	NS	NS	0.05	NS

HD: Huntington Disease; TMT: Trail Making Test; SDMT: Symbol Digit Modalities Test; NS: not significant.

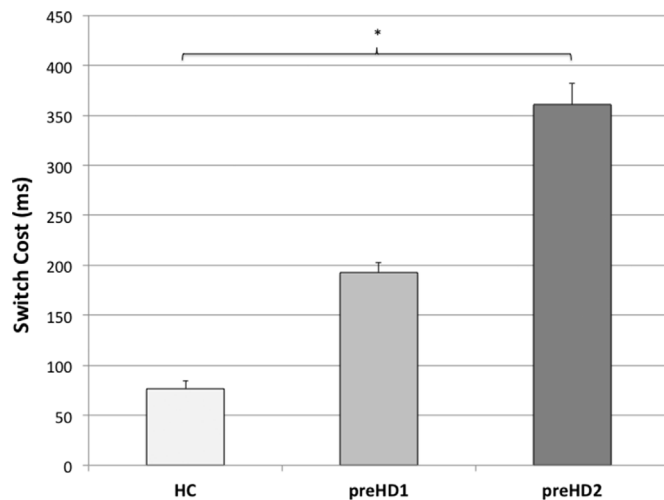


Fig. 2. Switch Cost (mean $\pm$ SEM) in all three groups.

Post-hoc comparison: * $p = 0.003$.

HC: Healthy Controls; pre-HD1: pre-manifest Huntington's Disease subjects with a Total Motor Score (TMS) ≤ 4 ; pre-HD2: pre-manifest HD subjects with a $5 \leq \text{TMS} \leq 9$.

hoc comparisons revealed a significant difference both between pre-HD1 and controls ($p = .001$) and pre-HD2 and controls ($p < .0001$) (see Fig. 3b).

Error proportion. With respect to accuracy, the one-way ANOVA revealed a significant Group effect ($F_{2,45} = 3.21$; $p = .05$; $\eta^2 p = 0.12$) indicating a higher proportion of errors in pre-HD1 Switch trials (1.40 ± 0.32) than pre-HD2 (1.27 ± 0.45) and control (1.35 ± 0.35) groups. *Post-hoc* comparisons revealed a significant difference between pre-HD1 and pre-HD2 groups ($p = .01$). No significant effects were observed in error proportion in repetition trials (see Fig. 4).

4. Discussion

To our knowledge, the present study has been the first to assess executive control in the premanifest HD by means of a task-switching protocol.

The neuropsychological screening assessment indicated a deficit of sustained attention (with and without interference) in all pre-HD subjects compared to HC; moreover, prodromal HD individuals (pre-HD2 group) showed an impairment of divided/visual attention and a higher number of intrusions in the semantic fluency test with respect to pre-HD1 group and HC.

Regarding task-switching abilities, our results showed that HD subjects had worse performance than controls, as indicated by an increase in both SC and RT. Statistical analyses carried out separately on switch and repetition trials showed that the performance of the pre-HD group was significantly worse than HC for both types of trials. In particular, a significant increase in SC only for pre-HD2 compared to pre-HD1 and HC was reported. Moreover, all subjects with pre-HD showed RT higher than HC in both repetition and switch trials. Regarding accuracy, pre-HD2 only showed a reduced error number in the execution of the task compared to the pre-HD1 group in switch trials. This phenomenon can be interpreted as a mechanism of behavioral compensation, since pre-HD2 could employ more time to make a decision compared to pre-HD1, and this could secure a higher accuracy rate.

The present results highlighted early and specific executive control impairment in premanifest disease, especially related to the ability to shift between different cognitive tasks in a rapid and flexible way, and adjust behavior to continuous and unexpected environmental changes.

These early difficulties in executive control processes could be explained as a consequence of altered functioning of the PFC and its

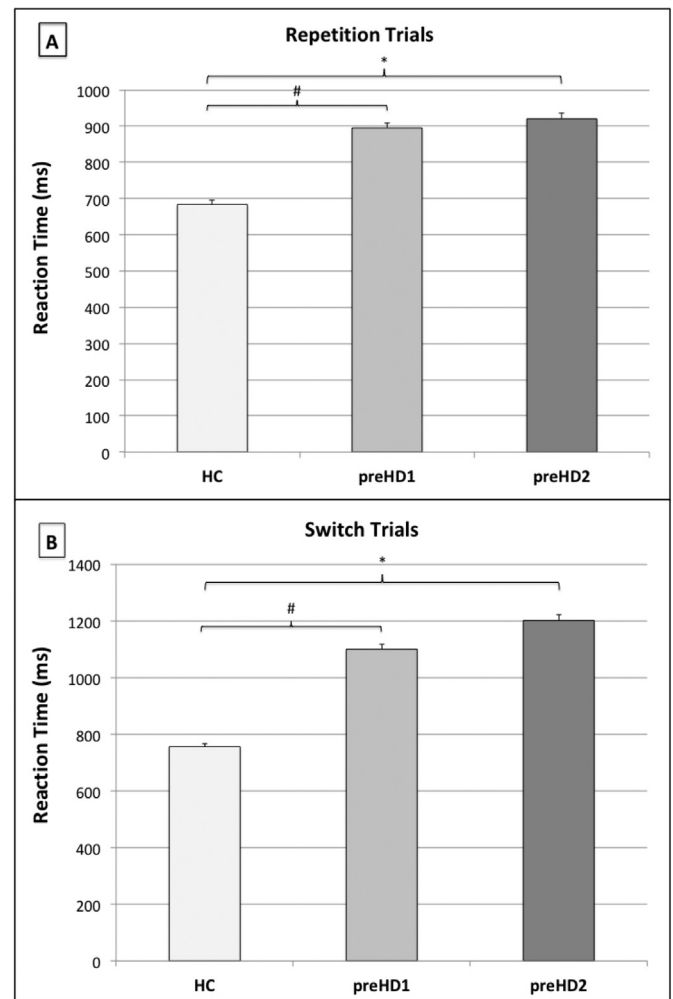


Fig. 3. A: Reaction time (in ms) in Repetition Trial (mean $\pm$ SEM) in all three groups.

Post-hoc comparison: * $p = 0.001$; # $p = 0.002$.

HC: Healthy Controls; pre-HD1: pre-manifest Huntington's Disease subjects with a Total Motor Score (TMS) ≤ 4 ; pre-HD2: pre-manifest HD subjects with a $5 \leq \text{TMS} \leq 9$.

B: Reaction time (in ms) in Switch Trial (mean $\pm$ SEM) in all three groups.

Post-hoc comparison: * $p = 0.0001$; # $p = 0.001$.

HC: Healthy Controls; pre-HD1: pre-manifest Huntington's Disease subjects with a Total Motor Score (TMS) ≤ 4 ; pre-HD2: pre-manifest HD subjects with a $5 \leq \text{TMS} \leq 9$.

cortical and subcortical connections. In HD, fronto-striatal circuits are particularly vulnerable to gene mutation [6]; different studies, indeed, showed early brain changes with a specific pattern of fronto-striatal alteration [5,29] that could be functionally linked to executive functioning (as, for example, to task-switching abilities). Different functional Magnetic Resonance Imaging (fMRI) studies [11,30] showed compensatory increased activity in a fronto-striatal network (including lateral prefrontal cortex, anterior cingulate cortex, caudate and putamen) over time in pre-HD during the working memory task, a sub-process of executive functions. These data suggest an early longitudinal change in the fronto-striatal network, with deterioration over time, which could explain executive dysfunction and behavioral changes (i.e. perseveration, irritability) in the early phase of the disease.

Executive functions are a set of cognitive processes necessary for the cognitive control of complex goal-directed behaviors and needed when we have to quickly and flexibly adapt to changing circumstances [14]. They include different cognitive sub-processes, i.e. inhibition, interference control, monitoring and cognitive flexibility. In clinical

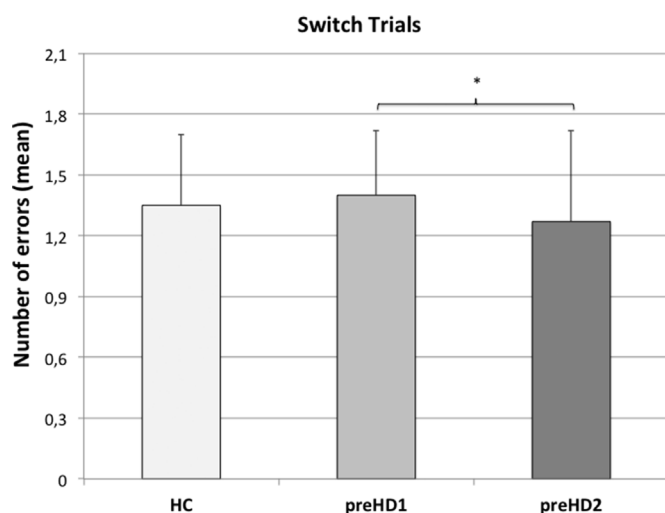


Fig. 4. Error proportion in Switch Trial (mean $\pm$ SEM) in all three groups. Post-hoc comparison: * $p = 0.01$.

HC: Healthy Controls; pre-HD1: pre-manifest Huntington's Disease subjects with a Total Motor Score (TMS) ≤ 4 ; pre-HD2: pre-manifest HD subjects with a $5 \leq \text{TMS} \leq 9$.

practice, the assessment of executive functioning is challenging, because a lot of time and many neuropsychological tests and/or scales are needed. Our study, however, highlighted that the task-switching protocol is a useful and comprehensive tool to detect early executive disorder in HD subjects without clear motor signs of the disease. These specific cognitive dysfunctions may deserve further longitudinal exploration in larger sized cohorts to potentially exploit new early markers of HD cognitive deterioration.

Our study has some limitations. First of all, our it is related to a self-reported questionnaire of psychological problems (SCL-90), which may suffer of the documented reduced subjects' awareness in HD subjects at any stage [9,31]. However, even considering such limitation, no subjects in our sample manifested with either psychiatric symptoms or severe psychological changes (e.g. depression, anxiety, irritability, obsessions, apathy, etc ...). Another limitation is due to the early impaired coordination, i.e. the abnormalities in finger tapping, potentially affecting pre-HD subjects [32]. However, in our opinion the association between valuable tasks exploring different fields of abnormalities such as cognitive (i.e. executive functions with task switching) and motor (i.e. finger tapping) impairment might reinforce the strategy to detect clinical markers to eventually transfer into clinical practice.

In conclusion, our findings highlighted an early impairment in executive control processes involved in task-switching performance in the pre-HD stage, which may be linked to early functional alteration of the fronto-striatal brain networks. Such abnormalities are more evident when pre-HD subjects start to show subtle motor manifestations, still unspecific and insufficient to define the clinical diagnosis of HD. Considering that these cognitive functions represent an essential domain to deal with life tasks, focused rehabilitation therapies including neurocognitive programs addressing such deficits should be taken into consideration in order to delay cognitive manifestation of the disease.

Contributors

SM developed the study concept, designed the study, interpreted data and drafted the manuscript. GD performed testing, data collection and data analysis. GC helped in developing the study concept and design and provided critical revision to the manuscript. FS helped in data interpretation and provided critical revision of the manuscript. All authors approved the final version of the manuscript for submission.

Declarations of interest

None.

Founding source

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