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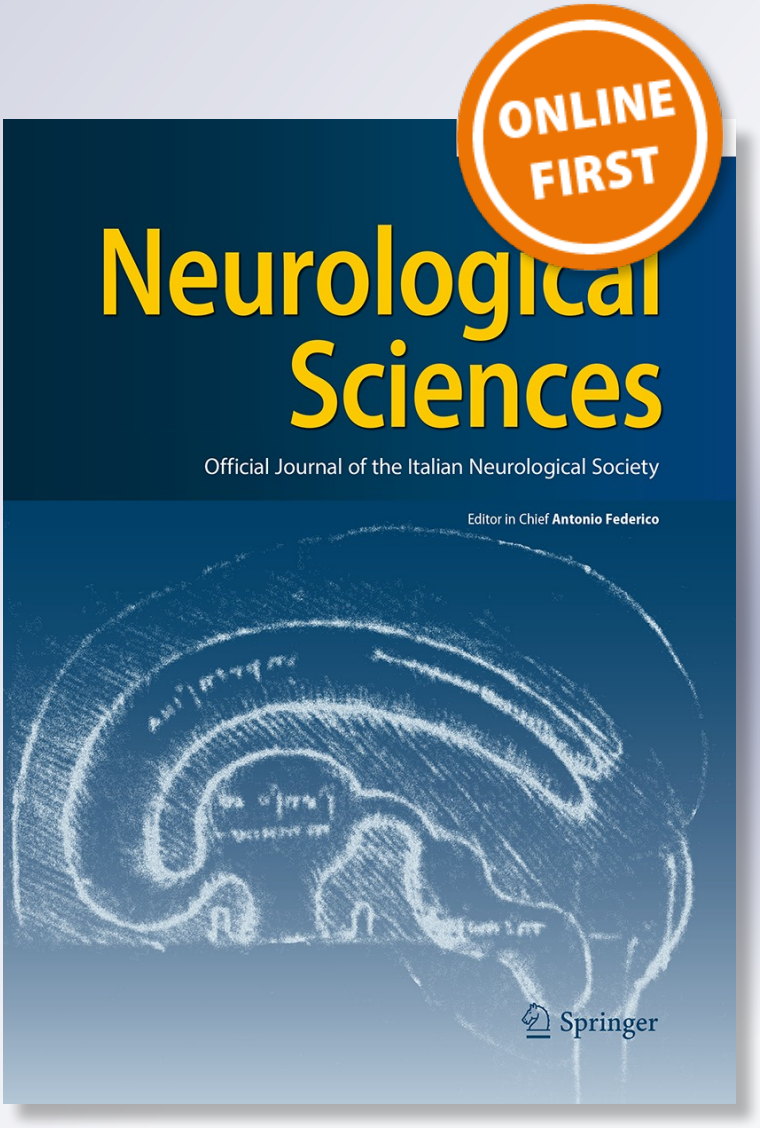

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ORIGINAL ARTICLE

Time perception impairment in early-to-moderate stages of Huntington's disease is related to memory deficits

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Abstract Huntington's disease (HD) primarily affects striatum and prefrontal dopaminergic circuits which are fundamental neural correlates of the timekeeping mechanism. The few studies on HD mainly investigated motor timing performance in second durations. The present work explored time perception in early-to-moderate symptomatic HD patients for seconds and milliseconds with the aim to clarify which component of the scalar expectancy theory (SET) is mainly responsible for HD timing defect. Eleven HD patients were compared to 11 controls employing two separate temporal bisection tasks in second and millisecond ranges. Our results revealed the same time perception deficits for seconds and milliseconds in HD patients. Time perception impairment in early-to-moderate stages of Huntington's disease is related to memory deficits. Furthermore, both the non-systematical defect of temporal sensitivity and the main impairment of timing performance in the extreme value of the psychophysical curves suggested an HD deficit in the memory component of the SET. This result was further confirmed by the significant correlations between time perception performance and long-term memory test scores. Our findings added important preliminary data for both a deeper comprehension of HD time-keeping deficits and possible implications on neuro-rehabilitation practices.

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Keywords Huntington's disease · Time perception · Episodic memory · Temporal bisection-task

Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by an expanded CAG repeat on the chromosome 4. HD's degeneration preferentially affects the medium spiny neuron of striatum (putamen and caudate) and consequently the cortico-striatal circuits of the prefrontal cortex generating typical movement disorders, psychiatric symptoms and several neuropsychological deficits [1]. The most common cognitive impairments in HD concern attention, executive functions, short- and long-term memory [2] as well as the time-keeping functions [3–5]. Timing deficit in HD has been mainly investigated in second and millisecond durations by tasks requiring a motor processing such as keeping spontaneous rhythm, time reproduction, self-paced timing tasks [3, 4]. In addition, recent evidences suggested deficit in time perception tasks [5]. These timing defects gradually worsen with disease progression and may further compromise the HD patients' motor performance since an optimal motor functioning requires a highly precise timing of the coordination of muscles involved in a movement [4]. HD timing deficit may be related to basal ganglia dysfunction since the dopaminergic neural networks of striatum, premotor and prefrontal cortical areas constitute the neural core of timing functions [6]. Specifically, taking into account the scalar expectancy theory (SET) [7], it is conceivable that basal ganglia were implicated in the internal clock functions which would be accomplished through three different components:

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pacemaker–accumulator unit, memory store and decision stage. The pacemaker–accumulator unit counts time intervals generating pulses which are added in the memory store. A slowdown in the internal clock pulses would produce a systematic time underestimation, whereas an increase in the pulses would yield a systematic time overestimation [8]. The memory store maintains the subjective time interval traces until the decision process. A deficit in memory storage and decision stage may be responsible for non-systematic reduction in the temporal sensitivity [8]. Although dysfunctions in temporal processing have been observed in HD patients [4, 5, 9], which component of the SET model is mainly responsible for HD temporal impairment has yet to be extensively explored. In keeping with this, the present work aims to shed light on the mechanisms underlying the HD perceptual timing deficit. Furthermore, since the role of basal ganglia in perceiving sub-second intervals is still debated [10, 11], we sought to clarify also whether HD may affect the processing of temporal information in the range of milliseconds. To our aim, we investigated time perception in symptomatic HD patients employing two temporal bisection tasks, one in the second durations and the other in the millisecond durations. The temporal bisection procedure has three advantages: it has been specifically developed in the SET framework [12], it does not place great demands on attentional processes and it is suitable to evidence time-perception deficits [13].

Furthermore, we correlated HD timing performance with both clinical variables and neuropsychological assessment to understand whether and to what extent the time perception performance is related to both cognitive functioning and disease progression.

Method

Subjects

Eleven symptomatic HD patients (six women) were recruited at the Neurological Unit of the Hospital of Careggi (Florence, Italy). Twenty-one healthy subjects matched for age served as controls (11 women).

UHDRS motor scores were assessed by an experienced neurologist. HD patients were all in early-to-moderate clinical stages (range UHDRS 13–45). Disease severity measures such as mean CAG-length, age of onset and duration of the disease were collected and reported in Table 1a. For each subject, an Italian short version of Verbal IQ (VIQ) test was collected. The Ethics Committee approved the study and all subjects gave written consent.

Neuropsychological assessment

Neuropsychological assessment evaluated attentional, executive, visuo-motor, verbal and short and episodic memory functions. Tests and results are shown in Table 1a.

Time perception assessment: temporal-bisection tasks

Two separate temporal-bisection tasks were employed for milliseconds (MS-task) and seconds (S-task). A 15-min interval divided the two tasks which were administered in counterbalanced order across the participants.

The stimuli were tones at 700 Hz binaurally presented through a wireless Karma® headset by using Presentation 0.50 software. Each task consisted of three phases: training session, learning assessment and test phase (see Fig. 1).

In the training session, participants had to listen to 10 subsequent presentations of the standard "Short" and "Long" durations, separated by random intervals from 1000 to 1500 ms. In the learning assessment, participants were requested to recognize standard "Long" and "Short" tones which were randomly presented ten times. Feedback for incorrect responses was given and the learning assessment was repeated until the 100 % correct responses were achieved. Afterward, in the test phase, participants were asked to say whether a randomly presented tone from a set of nine test stimuli was more similar to the standard "Short" or "Long" duration they had previously learned. After the participant's verbal response the experimenter pressed the appropriate response key ("Short" = "S"; "Long" = "L") on the keyboard. The nine test stimuli presented were the standard "Short" and "Long" together with seven intermediate stimuli. Every bisection task consisted of 20 trials for each of the nine stimuli. No feedback was given about the accuracy of the responses during the test phase.

In the millisecond-task (MS), the standard Short tone was 400 ms (T1) and the standard "Long" tone was 800 ms (T9). The seven intermediate stimuli were: 450 ms (T2), 500 ms (T3), 550 ms (T4), 600 ms (T5), 650 ms (T6), 700 ms (T7) and 750 ms (T8).

In the second-task (S), the standard Short tone was 1000 ms (T1) and the standard Long tone was 2000 ms (T9). The seven intermediate stimuli were: 1125 ms (T2), 1250 ms (T3), 1375 ms (T4), 1500 ms (T5), 1625 ms (T6), 1750 ms (T7) and 1875 ms (T8). For details see Fig. 1.

Data analysis

Since both small sample sizes and some data from neuropsychological tests and temporal-bisection task were non-normally distributed, we performed statistical analysis with non-parametric tests. Specifically Mann–Whitney

Table 1 A. Mean and SDs of demographic, clinical and neuropsychological data of HD patients and controls with Mann–Whitney *U* results and Kendall's tau correlation coefficient (τ) with the bisection parameters for milliseconds (DL-MS, WR-MS) and seconds (DL-S, WR-S) and the average proportion of average proportion of "Long" responses in T1, T2 and T9. B. Mean and SD of bisection parameters for milliseconds (DL-MS, WR-MS) and seconds (DL-S, WR-S) for HD patients and controls

A

	HD patients mean (SD)	Controls mean (SD)	Mann–Whitney *U* *F* (gdl)	Kendall's tau correlation coefficient (τ)						
				T1 (mean MS-S)	T2 (mean MS-S)	T9 (mean MS-S)	DL-MS	WR-MS	DL-S	WR-S
Demographic data										
Age (years)	55.54 (11.80)	54.10 (12.40)	108.50	0.15	0.21	0.23	0.09	0.09	0.28	0.31
Clinical data										
Age of onset	51.00 (10.91)			0.33	0.38	0.08	0.35	0.32	0.47*	0.50*
Duration of disease (years)	4.55 (2.02)			0.37	0.08	0.17	0.08	0.15	0.19	0.22
CAG-length	43.45 (2.35)			−0.16	−0.06	−0.14	−0.27	−0.19	−0.31	−0.23
UHDRS (motor score)	33.82 (16.70)			0.62**	0.47*	−0.27	0.46*	0.51*	0.47*	0.54*
Neuropsychological assessment										
MMSE	26.09 (1.93)	28.52 (1.63)	37.00**	−0.22	−0.06	0.04	−0.25	−0.28	−0.28	−0.09
Verbal QI	104.30 (7.29)	106.10 (8.53)	106.00	−0.10	−0.25	0.04	−0.20	−0.28	−0.19	−0.09
Attention and executive functions										
Trail making test A (TMT A)	114.55 (36.91)	60.29 (25.81)	23.50**	0.17	0.17	−0.34	0.24	0.16	0.16	0.13
Trail making test B (TMT B)	309.00 (120.95)	150.48 (59.79)	25.00**	−0.02	0.09	0.01	−0.06	−0.06	−0.27	−0.24
Wisconsin card sorting test (WCST)	46.91 (16.83)	29.43 (15.71)	54.00*	0.25	0.02	0.06	−0.18	−0.15	−0.04	0.07
Stroop W	64.18 (19.82)	30.67 (14.01)	19.50**	−0.17	−0.17	0.19	−0.13	−0.13	−0.13	−0.24
Stroop C	87.45 (13.33)	47.86 (13.56)	8.50**	−0.27	−0.11	0.17	−0.37	−0.36	−0.37	−0.26
Stroop CW	125.36 (32.26)	57.71 (14.41)	3.50**	−0.06	0.17	0.01	−0.16	−0.02	−0.09	−0.02
Visuo-motor and verbal abilities										
Symbol digit test (WAIS-R)	5.27 (2.10)	11.14 (3.45)	14.50**	−0.42	−0.26	0.12	−0.21	−0.14	−0.17	−0.21
Phonemic fluency	19.90 (6.27)	36.88 (10.27)	14.00**	0.04	0.01	0.17	−0.22	−0.15	−0.07	−0.04
Semantic fluency	13.21 (2.73)	22.85 (4.76)	14.00**	0.33	−0.06	−0.23	−0.20	0.06	0.13	0.17
Short-term memory and working memory										
Digit span forward	3.55 (0.52)	5.19 (1.08)	23.50**	0.44	0.35	−0.05	0.25	0.30	0.47	0.44
Digit span backward	2.64 (1.12)	4.38 (0.97)	25.50**	0.44	0.19	0.17	0.06	0.15	0.32	0.32
Serial position curve—recency	11.18 (3.49)	15.67 (2.46)	32.50**	−0.08	−0.31	0.02	−0.15	−0.30	0.01	0.04
Corsi block-tapping test—span	4.17 (0.62)	5.04 (0.57)	42.00**	0.24	0.22	0.45	0.02	0.10	0.29	0.25
Episodic memory										
Serial position curve—primacy	3.74 (2.30)	5.70 (1.80)	56.00*	−0.65**	−0.38	0.55*	−0.52*	−0.44	−0.63**	−0.59*
Buschke SR—long-term retrieval (LTR)	100.55 (23.96)	133.52 (16.50)	32.00**	−0.55*	−0.57*	0.39	−0.35	−0.27	−0.50*	−0.47*

Table 1 continued

A

	HD patients mean (SD)	Controls mean (SD)	Mann–Whitney U F (gdl)	Kendall's tau correlation coefficient (τ)					
				T1 (mean MS-S)	T2 (mean MS-S)	T9 (mean MS-S)	DL-MS	WR-MS	DL-S	WR-S
Buschke SR—consistent long-term retrieval (CLTR)	70.55 (32.07)	129.43 (16.62)	15.50**	−0.66**	−0.69**	0.38	−0.49*	−0.42	−0.49*	−0.53*
Buschke SR—delayed free recall (LTR)	5.63 (2.02)	7.96 (0.99)	28.50**	−0.31	−0.49*	0.59*	−0.50*	−0.22	−0.48*	−0.36
Corsi block-tapping test—supraspan	9.45 (4.71)	20.89 (2.73)	3.50**	−0.66**	−0.50*	0.56*	−0.46	−0.38	−0.46*	−0.49*

B

	PSE-MS mean (SD)	DL-MS mean (SD)	WR-MS mean (SD)	PSE-S mean (SD)	DL-S mean (SD)	WR-S mean (SD)
Controls	602.57 (36.61)	78.51 (31.47)*	0.13 (0.05)*	1464.93 (103.08)*	171.37 (50.57)*	0.12 (0.03)*
HD patients	640.46 (131.00)	144.32 (97.04)	0.22 (0.13)	1487.94 (223.00)	272.99 (149.34)	0.19 (0.11)

* <0.05

** <0.01

U tests were used to compare HD and control participants for age, VIQ and neuropsychological tests (see Table 1a).

Two separate Mann–Whitney U tests were employed to compare groups for the learning assessment time from the training session of both millisecond and second temporal-bisection tasks. Furthermore, data from the test session of the temporal-bisection tasks were separately computed for each participant as proportion of "Long" responses. These proportions were separately analysed with Mann–Whitney U tests in order to compare the group differences for each condition (MS- and S-bisection task) and stimulus duration (T1, T2, T3, T4, T5, T6, T7, T8, and T9). Furthermore, to detect within-group differences in condition (MS- and S-bisection task) and stimulus duration (T1, T2, T3, T4, T5, T6, T7, T8, and T9), we computed the Friedman test which represents the non-parametric alternative to the one-way ANOVA with repeated measures [14].

In addition, the proportion of "Long" responses were used to compute separate psychophysical functions for MS an S and to calculate for each subject the bisection parameters [8, 13]: point of subjective equality (PSE), difference limen (DL) and Weber ratio (WR). The PSE is the central value of the psychophysical curve. PSE indicates the stimulus duration at which the subject perceives the two durations to be the same, hence it is the value at which the subject will provide 50 % "Long" responses. The DL is an index of absolute temporal sensitivity calculated as half the difference between the durations providing 75 and 25 % "Long" responses. Since DL indicates the smallest duration difference that can be reliably discriminated, larger DL values indicate absolute lower temporal sensitivity. The WR is computed as DL/PSE and is a measure of relative temporal sensitivity: a higher Weber ratio corresponds to a lower temporal sensitivity. Bisection parameters of the two groups are reported in Table 1b. These bisection parameters (PSEs, DLs and WRs) were analysed with three separate Mann–Whitney U tests to compare groups (HD patients vs. controls).

Furthermore, to verify if timing performance may be related to general cognitive functioning and specifically to memory impairments, the Kendall's tau correlation coefficient was calculated between the time keeping indexes, which have proved impaired in HD patients, and (1) neuropsychological scores, (2) disease severity measures.

Results

Analysis on the training session of temporal-bisection tasks

The Mann–Whitney U tests on the learning time showed that, compared to controls, HD patients took more time to

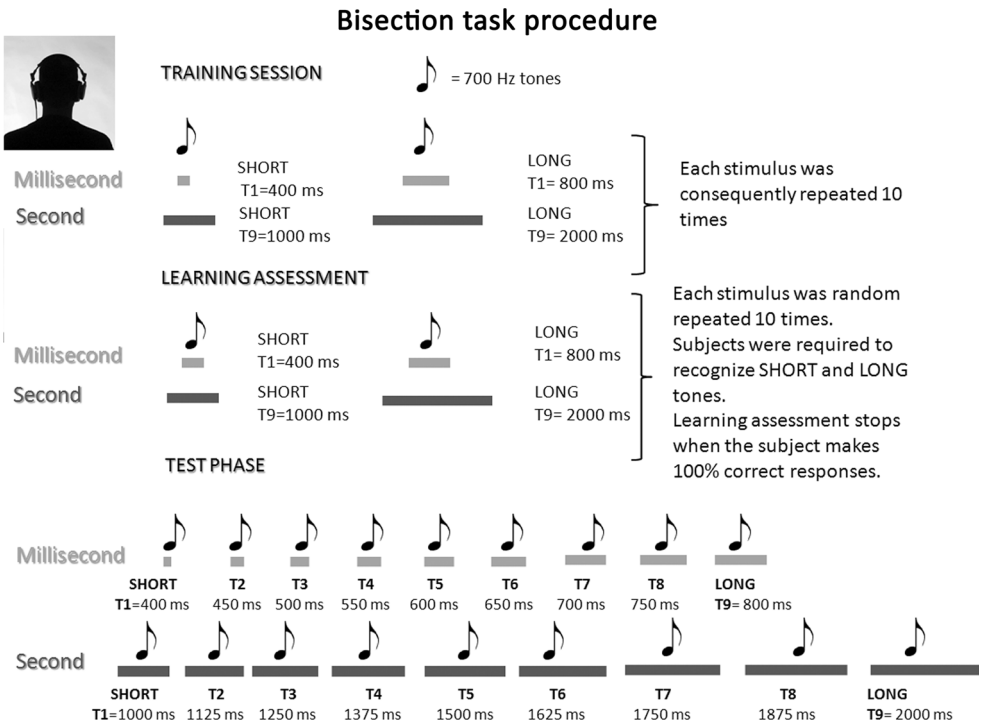

Fig. 1 Experimental procedure: training session, learning assessment and test phase. Proportion of "Long" responses plotted against stimulus durations (T1, T2, T3, T4, T5, T6, T7, T8, and T9) for HD patients and controls

achieve the 100 % of correct responses in the training sessions for both milliseconds ($U = 13.00$: $p < 0.01$) and seconds ($U = 18.00$: $p < 0.01$).

Analysis on the proportion of long responses

The Friedman tests, that were separately conducted within each group for each condition (milliseconds and seconds) and stimulus duration, indicated within both HD patients and controls a significant progressive growth of the proportions of "Long" responses as a function of the stimulus duration (see Table 2a). In addition, the Mann–Whitney U test (see Table 2b) showed that HD patients significantly overestimated short durations (MS-T1: $p < 0.03$; S-T1: $p < 0.04$; MS-T2: $p < 0.03$; S-T2: $p < 0.03$) and underestimated the standard "Long" duration (MS-T9: $p < 0.04$; S-T9: $p < 0.04$).

Hence, HD patients were mainly impaired in judging the extreme values of the psychophysical curve as shown in Fig. 2.

Analysis on the bisection parameters

The Mann–Whitney U tests revealed for both milliseconds and seconds higher DL (MS: $U = 62.00$, $p < 0.04$; S: $U = 60.00$, $p < 0.03$) and lower WR (MS: $U = 65.00$, $p < 0.05$; S: $U = 61.00$, $p < 0.04$) for HD patients compared to controls, whereas PSE values did not differ between groups (see Table 1b).

Correlations

Neuropsychological scores and disease severity measures were correlated (Kendall's tau correlation coefficient) with the bisection parameters (DL-MS, DL-S, WR-MS and WR-S) and the stimulus durations (T1, T2 and T9) in which HD patients were impaired. Since the proportion of "Long" responses did not statistically differ in MS and S conditions, we used in correlation the average proportion of "Long" responses in T1, T2 and T9 (i.e. T1 was the mean of T1-MS and T1-S proportions). See Table 1a for correlation results.

Discussion

The aim of the present study was twofold: (1) to explore the impaired timing mechanisms in early-to-moderate HD, taking into account the SET model; (2) to clarify whether HD affects in the same way the processing of seconds and milliseconds.

Intriguingly, our results revealed the same time perception deficits for seconds and milliseconds in early-to-moderate stages of HD. A still debated question is whether the neural substrates and circuitry involved in the temporal processing of intervals of very brief duration (milliseconds) differ from those underlying longer timing intervals (seconds-to-minutes range) [11, 15]. Specifically, one enduring issue concerns the contribution of frontal-striatal circuits

Table 2 A. Friedman's test results: the ranks of the scores for each stimulus duration and condition (millisecond = MS and second = S) in HD patients and controls with Chi-square, *df* and *p* value. B. Mann–Whitney *U* and *p* value (HD patients vs. controls) for each stimulus duration and condition (millisecond = MS and second = S)

A

Stimulus duration	HD patients		Controls	
	MS Ranks	S Ranks	MS Ranks	S Ranks
T1	2.23	2.00	1.43	1.43
T2	2.36	2.12	1.88	1.83
T3	3.09	2.50	2.86	2.95
T4	4.05	4.18	4.21	3.95
T5	4.18	5.05	4.81	5.26
T6	5.77	6.23	6.07	6.14
T7	6.73	7.14	7.26	7.19
T8	8.23	7.82	7.79	7.76
T9	8.36	7.95	8.69	8.48
	$N = 11$	$N = 11$	$N = 21$	$N = 11$
	Chi-square = 67.90	Chi-square = 70.61	Chi-square = 158.20	Chi-square = 153.83
	$df = 8$	$df = 8$	$df = 8$	$df = 8$
	Asymp.Sign = 0.00**	Asymp.Sign = 0.00**	Asymp.Sign = 0.00**	Asymp.Sign = 0.00**

B

Stimulus duration	HD patients vs. controls			
	MS		S	
	Mann–Whitney *U*	*p*	Mann–Whitney *U*	*p*
T1	59.50	0.025*	61.50	0.031*
T2	59.50	0.025*	60.00	0.027*
T3	78.50	0.144	99.00	0.531
T4	104.50	0.667	107.00	0.755
T5	110.50	0.842	103.50	0.639
T6	96.00	0.437	90.50	0.372
T7	81.50	0.180	112.00	0.907
T8	83.50	0.208	102.50	0.611
T9	62.00	0.034*	62.50	0.034*

* <0.05

** <0.01

vs. cerebellum in perceiving sub-second intervals [11, 16]. Our results agree with studies that suggested a main involvement of the basal ganglia in the temporal processing of very brief durations [10, 17]. Furthermore, when considering the bisection parameters, our HD subjects showed higher DL and WR values compared to controls, whereas the PSE did not differ between clinical and control sample. In this vein, our results of a more fluctuating performance in HD patients compared to controls are in agreement with previous studies on unilateral and focal lesions of the basal ganglia [18] cerebellar lesions [19], PD [10, 13], and Alzheimer's disease patients [12]. Remarkably, our data supplement previous studies that employed different timing tasks [4] evidencing a non-systematically reduced temporal sensitivity in HD patients. Hence, taking into account the SET framework [7], our finding may not be due to a defect in the pacemaker–accumulator unit of the internal clock. In fact, changes in the internal clock pulse rate would produce a systematic over- or underestimation across all the psychophysical curve values displacing also the central value (PSE). Rather, the non-systematical impairment of temporal sensitivity may reasonably be attributed to a dysfunction in memory and/or decision stage [12]. However, the results from the analysis on the proportion of "Long" responses favour the hypothesis that memory deficits actually shaped the time keeping impairments. In fact, HD

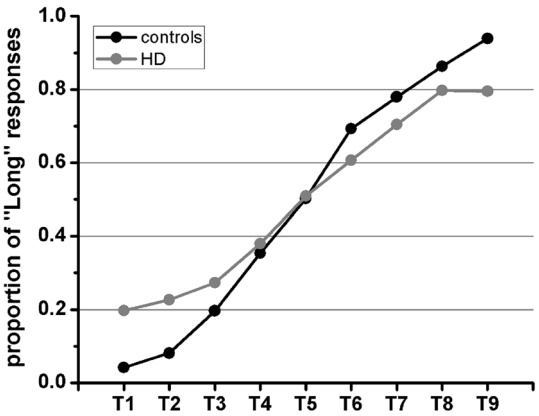

Fig. 2 Psychophysical functions for the two temporal bisection tasks: mean proportion of long responses plotted against comparison stimulus duration for both millisecond (MSe) and second (Se) conditions in controls and HD subjects

subjects were impaired with respect to controls in the extreme values of the psychophysical curve (T1, T2 and T9) showing a bi-directional shift. Specifically, HD patients overestimated the "Short" stimuli durations and underestimated the "Long" ones. This pattern of results resembles a deficit already described in Parkinson's disease (PD) patients and called "migration effect" [20–23]. This effect, which may occur when subjects are required to learn two different time durations, consists in the tendency to overestimate the learned short intervals and underestimate the long ones [20–23]. The "migration effect" results from a mutual attraction between the two learned intervals and indicates a dysfunction in memory for time since the two temporal representations are mixed in long-term memory [21]. In agreement with previous studies on PD patients [21], the assumption that memory retrieval is required for performance during both encoding and decoding sessions, led us to attribute migration in HD patients to a dopamine-dependent dysfunction of updating temporal memory. Specifically, it may be that the dysfunction of the DLPFC dopaminergic system prejudices the correct interaction between the transient working memory of the SET model and the permanent (episodic memory) storage of the outcome from the accumulator [11]. In keeping with this, a deficit in time representation memory may well account for both our results in HD patients: the non-systematic reduction of temporal sensitivity [8] and the bi-directional shift that affected the extreme values of the psychophysical curve [20, 21, 24]. Remarkably, the hypothesis that the timing deficits may be related to memory impairments is further supported by both the evidence of incremented learning times in training session and the significant correlation between memory test scores and timing performance in our HD patients, in agreement with previous studies on PD subjects [25]. In fact, although our clinical sample was globally impaired in neuropsychological functioning with respect to controls, the time perception performance of HD patients significantly correlated only with episodic memory scores. The long-term memory impairment agrees with the literature on HD [26], and it may be associated with the progressive disruption to the dopaminergic loops between prefrontal cortex and striatum [26]. Similarly, the temporal memory dysfunction we found in early-to-moderate HD patients may be related to the damage progression that prematurely affects the dorsomedial striatum and consequently the dorsolateral prefrontal cortex (DLPFC). This area is a specialized system for the active memory-representation maintenance [27], retrieval of learned material [28] as well as for the interconnection between working memory and episodic memory [29]. Further investigations might shed light on the exact nature of the HD's memory deficit clarifying whether the dysfunction affects the temporal representation maintenance or, more probably, the memory encoding and updating operations that are implemented by the memory system in the SET. This issue is central for a deeper comprehension of HD time-keeping deficits and it may also have a clinical relevance [30]. In fact, considering that in our clinical sample the timekeeping performance significantly correlated with motor impairment (UHDRS), in agreement with studies which showed that timing defects may aggravate motor behaviours, the connection between episodic memory, timing performance and motor dysfunction progression deserves further attention for possible implications on neuro-rehabilitation practices.

Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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