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Deficits in temporal processing correlate with clinical progression in Huntington's disease

P. V. Agostino[1] | E. M. Gatto[2] | M. Cesarini[2] | J. L. Etcheverry[2] | A. Sanguinetti[2] | D. A. Golombek[1]

[1]Department of Science and Technology, National University of Quilmes/ CONICET, Bernal, Buenos Aires, Argentina

[2]Instituto de Neurociencias de Buenos Aires, INEBA, Bernal, Buenos Aires, Argentina

Correspondence
P. V. Agostino, Departamento de Ciencia y Tecnología, Universidad Nacional de Quilmes, Bernal, Buenos Aires, Argentina.
Email: pagostino@unq.edu.ar

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Objectives: Precise temporal performance is crucial for several complex tasks. Time estimation in the second-to-minutes range—known as interval timing—involves the interaction of the basal ganglia and the prefrontal cortex via dopaminergic–glutamatergic pathways. Patients with Huntington's disease (HD) present deficits in cognitive and motor functions that require fine control of temporal processing. The objective of the present work was to assess temporal cognition through a peak-interval time (PI) production task in patients with HD and its potential correlation with the Unified Huntington's Disease Rating Scale (UHDRS).

Materials and methods: Patients with molecular diagnosis of HD and controls matched by age, sex and educational level (n=18/group) were tested for interval timing in short- (3 seconds), medium- (6 seconds) and long (12 seconds)-duration stimuli.

Results: Significant differences were observed in the PI task, with worse performance in HD compared to controls. Patients underestimated real time (left-shifted Peak location) for 6- and 12-second intervals ($P<.05$) and presented decreased temporal precision for all the intervals evaluated ($P<.01$). Importantly, a significant correlation was found between time performance and the UHDRS ($P<.01$). Patients' responses also deviated from the scalar property.

Conclusions: Our results contribute to support that timing functions are impaired in HD in correlation with clinical deterioration. Recordings of cognitive performance related to timing could be a potential useful tool to measure the neurodegenerative progression of movement disorder-related pathologies.

KEYWORDS
dopamine, Huntington's disease, medium spiny neurons, timing and time perception

1 | INTRODUCTION

Temporal processing in the range from seconds to minutes, known as interval timing, is crucial for multiple cognitive processes such as memory, learning and decision-making.[1] In most species, interval timing follows the scalar property, which implies that the error in time estimation is proportional to the estimated duration.[1,2] Several lines of evidence point to the basal ganglia (BG) as the primary brain area implicated in such temporal processing.[3] Indeed, recent findings argue for the involvement of cortico-striatal circuits, controlled by dopaminergic modulation of oscillatory activity and lateral connectivity. Medium spiny neurons (MSNs) detect the coincident activity of specific beat patterns of cortical oscillations.[3,4] Manipulations of these dopaminergic systems are able to modify interval timing by altering the speed and other properties of the internal clock.[5] The importance of cortico-striatal pathways for interval timing has been demonstrated

P.V. Agostino and E.M. Gatto contributed equally.

using different methodologies, such as fMRI studies, striatal lesions, drugs that affect dopamine (DA) signaling and genetic manipulations that affect the DA system,[2,5,6] as well as striatal neuronal activity recordings.[7] Moreover, interval timing is altered in several disorders associated with pathological dopaminergic function, including schizophrenia, Parkinson's disease (PD), attention-deficit hyperactivity disorder (ADHD) and multiple system atrophy.[8–10] For example, patients with PD exhibit important deficits on temporal reproduction tasks, which are attenuated by levodopa administration.[8] Furthermore, some dopamine-related gene polymorphisms—such as DRD2/ANKK1-Taq1a, COMT Val158Met and DAT 3' VNTR—have been associated to timing behavior.[11,12]

Specifically, Huntington's disease (HD) is an autosomal-dominant genetic disorder caused by an expansion in the normal number of CAG (glutamine) repeats (generally >40) in exon 1 of the huntingtin (HTT) gene.[13] Mutant Huntingtin causes abnormal synaptic transmission in HD. In the striatum, MSNs are most affected and degeneration of these neurons occurs progressively.[14] Clinically, patients with HD present progressive motor dysfunction, cognitive decline and psychiatric disturbance with the age of onset inversely related to the repeat length.[15,16] Cognitive impairment may develop years earlier than motor dysfunction, deteriorates over time and accounts for a significant portion of reduced functional capacity in patients with HD.[17] Alterations in the normal functioning of cortico-striatal circuits may be the mechanism underlying impaired cognition in early HD.[18]

Variability in temporal processing has been previously described in patients with HD.[19–23] For example, decreased performance in a time estimation task but not in a time discrimination task was observed in premanifest patients with HD, while both tasks were affected in manifest patients with HD.[19] Moreover, precision in a single interval production task has been reported to be lower in manifest and premanifest patients with HD compared to controls; however, no differences were seen in accuracy across groups.[20] Timing precision was also reported to be decreased in HD for very short intervals, such as 550 milliseconds.[22]

The objective of the present work was to assess interval timing accuracy and precision in a peak-interval time (PI) production task in patients with molecular confirmation of HD and their respective controls. Temporal accuracy, precision and application of the scalar property were evaluated in both groups. To examine whether timing performance in patients with HD correlated with clinical manifestations, variability in interval timing was correlated with the UHDRS.

2 | MATERIALS AND METHODS

2.1 | Subjects

Thirty-six participants were examined: 18 patients with HD and 18 matching (age, sex and educational level) healthy controls (see Table 1). For patients with HD, mean expanded allele was 42.94±1.91 and average disease duration was 7 years (range 1-12 years). UHDRS motor score [24] was also assessed (see Table 2). Some patients (specified in Table 2) were treated with low doses of neuroleptics (olanzapine ≤10 mg/d, quetiapine ≤50 mg/d and risperidone ≤2 mg/d). The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All subjects provided informed consent before study participation. This study was approved by the Ethics Committee of the National University of Quilmes (UNQ) and the Institute for Neurosciences of Buenos Aires (INEBA).

TABLE 1 Descriptive demographical and clinical data of patients with HD and controls

	Patients with HD (mean±SD)	Controls (mean±SD)
Sample size	N=18	N=18
Male/female ratio	5/13	11/7
Age (years)	48.50±13.62	41.89±13.75
CAG repeat length	42.94±1.91	NA
Age at onset	40.85±13.63	NA
UHDRS total	39.83±25.27	NA
MoCA	25.38±3.02	29.40±0.84

Ref: NA, not applicable.

2.2 | Interval timing protocol

The procedure and data collection was performed on a laptop computer (PC). Participants were seated comfortably on a chair facing the computer screen. The participants' preferred hand rested on the spacebar of the computer keyboard. The spacebar was used for response production. The Enter key was also used to initiate and to end trials. The PI task was modified from Fortin et al.[25] Briefly, the protocol consisted in a visual task, in which a blue square together with the word "Observe" was presented for the target interval. There was a 500-millisecond pause, and then a red square appeared together with the word "Produce". After judging that the duration of the red square matched the duration of the previous blue square, the participants responded by pressing the spacebar. Subjects could then terminate the trial by pressing the Enter key. The program included an automatic termination of the trial if the stimulus (red square) lasted for three times the target duration. Target intervals were of 3, 6 and 12 seconds, evaluated in three separate 24-trial blocks. To familiarize participants with the task, four practice trials were included at the beginning of each block. These trials were followed by a feedback sign, showing a histogram with the response distribution and its position relative to the target duration. Practice trials were not included in the data analysis. Overall, the experiment lasted for approximately 30 minutes. Participants were instructed to avoid counting or to use any other process of interval subdivision—such as foot tapping, for example.

2.3 | Reaction time task

Sustained attention was assessed by a computerized test of psychomotor response to a stimulus, adapted from Palm PVT 2.0.1., Walter Reed Army Institute of Research.[26] The test was adapted and validated in our laboratory for use in laptops and requires sustained

TABLE 2 Individual data from patients with HD

HD patient[a]	CAG repeat length	UHDRS total	Medication[b]	Peak location 3 seconds (s)	Peak location 6 seconds (s)	Peak location 12 seconds (s)
1 (F)	42	37	Yes	3.31	4.77	10.43
2 (F)	44	61	Yes	2.59	6.25	11.98
3 (F)	44	32	Yes	3.50	6.07	11.59
4 (M)	45	24	Yes	2.84	5.56	13.17
5 (F)	44	45	No	2.56	5.82	11.44
6 (F)	43	24	No	2.59	5.78	11.50
7 (M)	42	27	Yes	2.79	4.96	9.85
8 (F)	41	32	Yes	3.05	6.03	12.71
9 (M)	47	48	Yes	2.81	5.48	11.67
10 (F)	44	49	Yes	4.38	6.10	11.25
11 (M)	40	28	Yes	3.59	6.14	12.17
12 (M)	43	6	No	3.16	5.52	11.28
13 (F)	41	5	No	3.01	6.23	12.83
14 (F)	43	2	No	3.51	6.10	12.07
15 (F)	41	77	No	3.33	5.73	12.02
16 (F)	41	78	No	2.59	5.79	11.50
17 (F)	45	90	No	2.82	5.65	9.79
18 (F)	43	52	No	3.02	6.07	10.48

[a]F, female; M, male.
[b]Neuroleptics at small doses (olanzapine ≤10 mg/d, quetiapine ≤50 mg/d and risperidone ≤2 mg/d).

attention and response speed for a period of 5 minutes. The response speed was measured by pressing any key on the computer to the random appearance of a stimulus (black circle) on a white screen.

2.4 | Motor assessment

The severity of motor dysfunction was assessed using the motor examination from the UHDRS.[24] Total scores range between 0 and 124, with higher scores signifying greater motor dysfunction.

2.5 | Cognitive assessment

The Montreal Cognitive Assessment (MoCA), scored from 0 to 30,[27] was performed in both patients and controls. The MoCA consists of 12 individual tasks grouped into cognitive domains including 1—visuospatial/executive functioning, 2—naming, 3—attention, 4—language, 5—abstraction, 6—memory and 7—orientation. A total score from 26 to 30 indicates no cognitive impairment.

2.6 | Data analysis

2.6.1 | Interval timing (PI task)

Data were fit to a Gaussian function, and the best-fit parameters Peak location (X_0), Peak amplitude (a) and Peak width (b) were calculated as previously reported.[6,28] Moreover, the S1 (Start) and S2 (Stop) rate indexes were determined by taking the responses in a specified window (20% of the target duration) just prior to (S1) or after (S2) the target time as a ratio of overall responses within the first (S1) or second (S2) half of the trial (Figure 2A). Windows were 600, 1200 and 2400 milliseconds for the 3-, 6- and 12-second intervals, respectively. For example, the S1 rate index for the 3-second target duration was defined by the responses occurring during the 600 milliseconds period just prior to the target time (i.e. milliseconds 2400-3000) divided by the overall responses for the first half the trial (i.e. milliseconds 0-3000). Similarly, the S2 rate index for the 3-second target duration was defined by the responses occurring during the 600 milliseconds period just after the target time (i.e. milliseconds 3000-3600) divided by the overall responses for the second half the trial (i.e. milliseconds 3000-6000). See references [28,29] for additional details.

2.6.2 | Reaction time task

The speed of psychomotor response was quantified by the average response time (milliseconds).

2.6.3 | MoCA test

Scores from controls and patients with HD were compared.

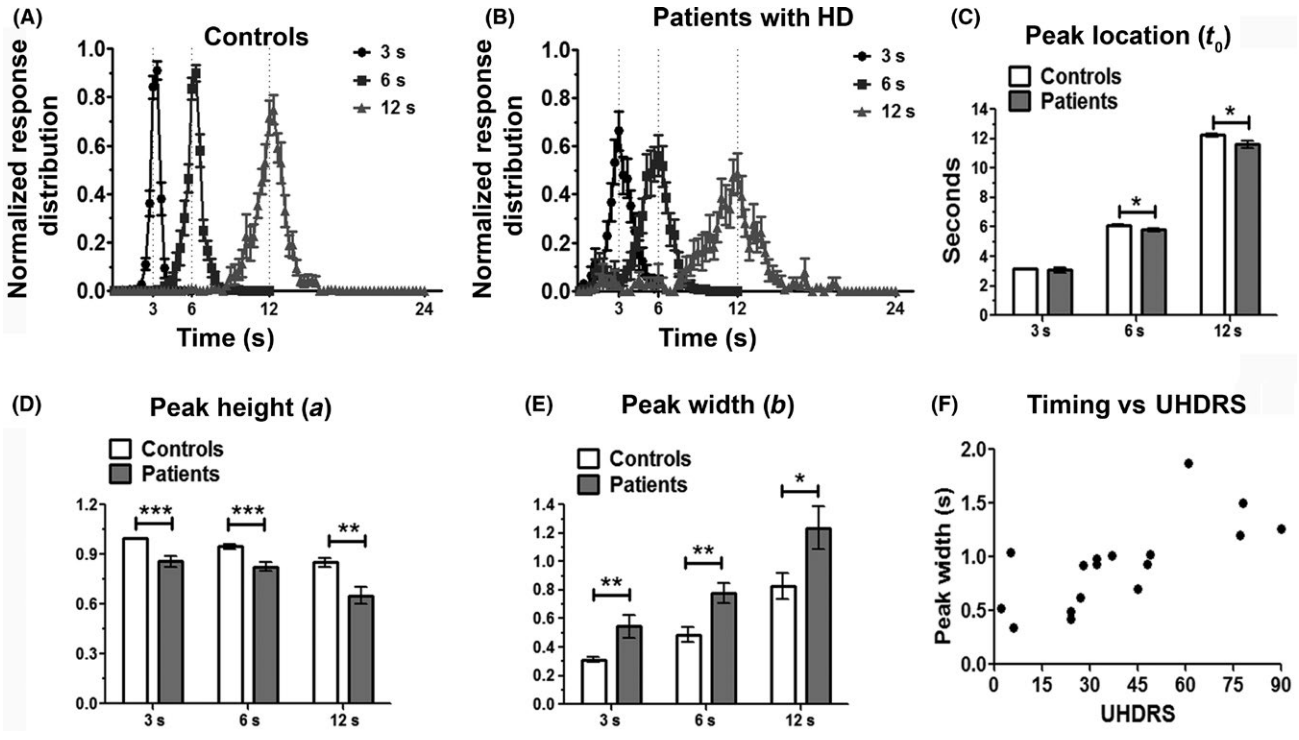

FIGURE 1 Peak-interval timing in patients with HD. Normalized response distribution of PI trials as a function of time in the trial in (A) controls and (B) patients with HD. Dashed lines indicate target times (3, 6 and 12 seconds). (C) to (E) display the mean best-fit parameter values from the Gaussian fits. (C) Peak location, (D) Peak height and (E) Peak width. Data are shown as mean±SEM. ***P<.001, **P<.01, *P<.05, two-tailed t-test, n=18/group. (F) Relationship between precision (Peak width) and UHDRS in HD subjects at all three target intervals (n=18). Pearson correlation coefficient=0.72, P=.001.

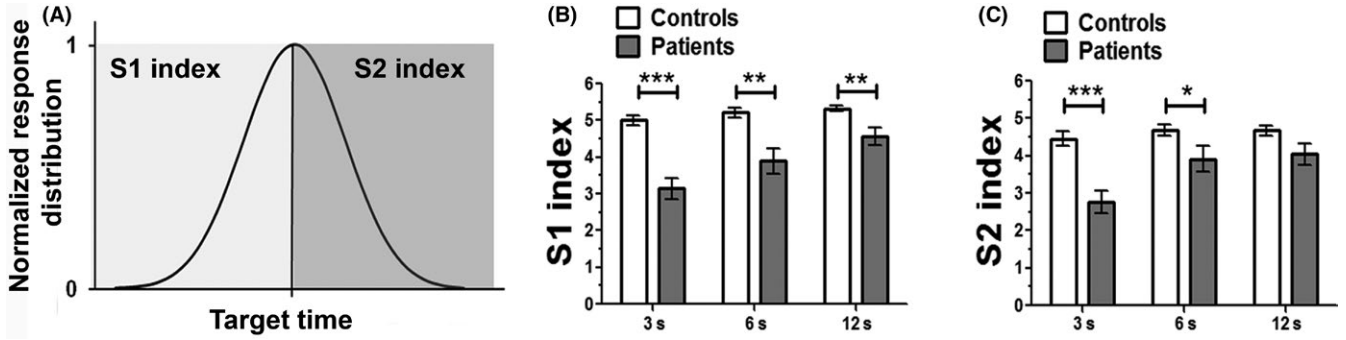

FIGURE 2 S1 (Start) and S2 (Stop) rate indexes in patients with HD. (A) Rate indexes were determined by taking the responses in a specified window just prior to (S1) or after (S2) the target time as a ratio of overall responses within the first (S1) or second (S2) half of the trial. (B) Mean S1 rate index. (C) Mean S2 rate index. Data are shown as mean±SEM. ***P<.001, **P<.01, *P<.05, two-tailed t-test, n=18/group.

Statistical analyses were performed using GraphPad Prism (GraphPad Software Inc., San Diego, CA, USA). In all cases, the alpha level was set at P<.05.

3 | RESULTS

3.1 | Sample characteristics

Table 1 shows the general profile of both groups. There were no significant differences in age (t_{34}=1.449, P=.1566, two-tailed t-test, n=18/group). Results from MoCA evaluation indicated higher scores for controls compared to patients with HD (t_{34}=4.058, P=.0007, two-tailed t-test, n=18/group). However, average MoCA score from patients was >25, indicating absence of severe cognitive impairment.[27]

3.2 | Patients with HD exhibit decreased accuracy and precision in the peak-interval (PI) task

Figure 1 summarizes the behavioral performance during the PI task. The normalized response distributions plotted as a function of signal duration are illustrated in Figure 1A,B for controls and patients with HD, respectively. Responses were fitted to a Gaussian function to obtain the best-fit parameters: Peak location, Peak amplitude and Peak width (Figure 1C-E). Peak location is taken as an estimate of the accuracy of interval timing, while the width (or spread) of the response function is taken as an estimate of the precision of timing.[5] Results indicate significant differences between groups in these parameters. In this sense, patients with HD exhibited a left-shifted Peak location compared to controls for the 6- and 12-second target intervals (Figure 1C; t_{34}=0.5741, P=.5697 for 3 seconds; t_{34}=2.449, P=.020 for 6 seconds; and t_{34}=2.460, P=.0191 for 12 seconds; two-tailed t-test), as well as a decreased Peak amplitude for all the intervals evaluated (Figure 1D; t_{34}=4.066, P=.0003 for 3 seconds; t_{34}=4.361, P=.0001 for 6 seconds; and t_{34}=3.502, P=.0013 for 12 seconds; two-tailed t-test). Patients also presented a larger Peak width (higher dispersion) for all target intervals (Figure 1E; t_{34}=2.749, P=.0095 for 3 seconds; t_{34}=3.462, P=.0015 for 6 seconds; and t_{34}=2.335, P=.0256 for 12 seconds; two-tailed t-test). Therefore, patients with HD had a significant tendency to underestimate real time as compared to controls (decreased timing accuracy) and presented higher variability (decreased timing precision).

As some patients were under medication with small doses of neuroleptics, Table 2 presents the observed Peak location for individual patients for all three intervals evaluated. There were no specific effects of medication on Peak location; that is, the observed changes in interval timing accuracy did not correlate with the medication taken by some of the patients.

3.3 | Timing variability in the PI task correlates with clinical progression in patients with HD

Importantly, variability in the PI task—expressed as averaged Peak width for all three target intervals—correlated with UHDRS (Figure 1F, Pearson correlation coefficient=0.72, P=.001, n=18). Moreover, Peak width did not correlate with MOCA evaluation (P=.096, data not shown).

3.4 | Patients with HD present decreased S1 and S2 indexes in the PI task

Furthermore, the mean S1 and S2 indexes were used to evaluate learning of the Start and Stop responding, respectively. As illustrated in Figure 2A, these indexes were determined by taking the responses in a specified window just prior to (S1) or after (S2) the target time as a ratio of overall responses within the first (S1) or second (S2) half of the trial (see Methods). The higher these indexes, the better timing mechanism. The S1 index (Start) was significantly higher for controls compared to patients with HD for all three intervals evaluated (Figure 2B; t_{34}=5.944, P<.0001 for 3 seconds; t_{34}=3.565, P=.0011 for 6 seconds; and t_{34}=2.982, P=.0052 for 12 seconds; two-tailed t-test). Similarly, the S2 index (Stop) was significantly higher for controls for the 3- and 6-second target intervals, while it did not reach significant levels for the 12-second target interval (Figure 2C; t_{34}=4.802, P<.0001 for 3 seconds; t_{34}=2.083, P=.0449 for 6 seconds; and t_{34}=1.923, P=.0629 for 12s; two-tailed t-test). These results indicate that patients were more disperse than controls in their responses, another indication of lower precision in the PI task.

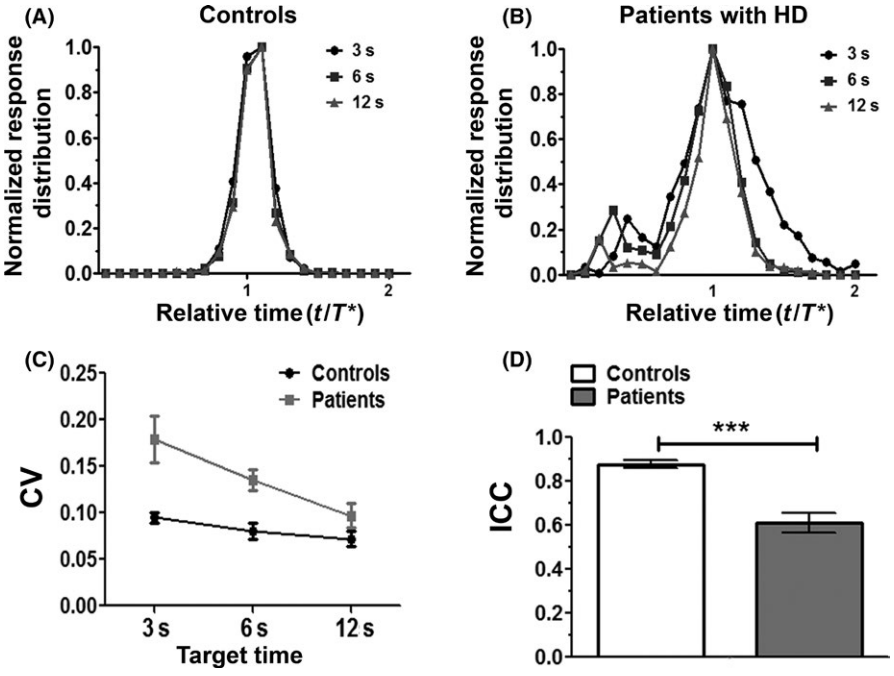

FIGURE 3 Scalar property in patients with HD. Normalized response distributions plotted as a function of relative time for (A) controls and (B) patients with HD. (C) Coefficient of variation (CV) across target intervals for controls (circles) and patients with HD (squares). *P*<.001 for groups, two-way ANOVA. (D) Intraclass correlation coefficient (ICC). Data are shown as mean±SEM. ***P<.001, two-tailed *t*-test, n=18/group.

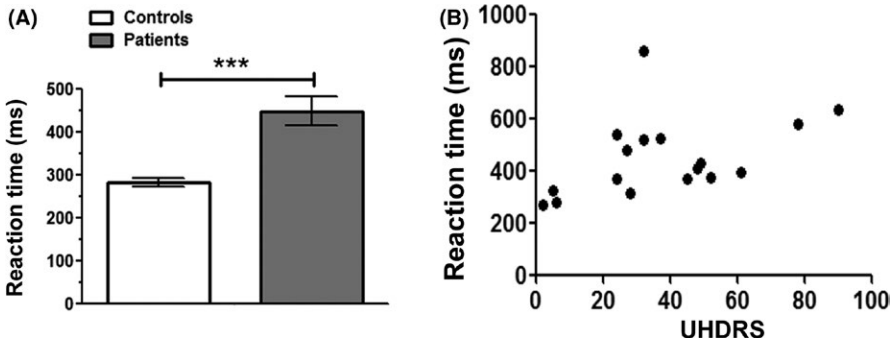

FIGURE 4 Reaction time in patients with HD. (A) Reaction time (expressed in milliseconds) in controls and patients with HD. Data are shown as mean±SEM. ***P<.001, two-tailed *t*-test, n=18/group. (B) Relationship between reaction time and UHDRS in HD subjects (n=18). Pearson correlation coefficient=0.64, *P*=.08.

3.5 | Timing in patients with HD deviates from the scalar property

We also examined the coefficient of variation (CV), the ratio between estimation error (Peak width) and estimation accuracy (Peak location or Peak time), which is shown to be relatively constant in a large range of timed durations in humans and animals.[2] This scalar property reflects the Weber's Law applied to interval timing, which implies superimposition of response functions when normalizing these responses to the target duration.[30] Figure 3 illustrates the normalized response functions rescaled (proportional) to the target time for controls (Figure 3A) and patients with HD (Figure 3B). Controls presented superimposition of their response distributions for all the three intervals tested, in contrast to patients with HD. Moreover, the CVs were constant for the PI task in controls (reflecting the scalar property), but were increased in the short durations (3 and 6 seconds) for patients (Figure 3C). To further evaluate the scalar property, we then calculated the intraclass correlation coefficient, ICC, for each subject's normalized distribution. ICC values greater than 0.85 are indicative of excellent superposition of normalized functions for all time bins, with a value of 1.0 indicating perfect scalar timing.[31] Patients with HD presented significantly lower ICC values compared to controls (Figure 3D, t_{34}=5.667, *P*<.0001, two-tailed *t*-test, n=18/group), indicating a deviation of the scalar property in these patients.

3.6 | Patients with HD exhibit increased reaction time

Results from the reaction time task yielded significant differences between groups, with higher reaction time in patients with HD (Figure 4A, t_{34}=4.635, *P*<.0001, two-tailed *t*-test, n=18/group). However, reaction time did not correlate with UHDRS (Figure 4B, Pearson correlation coefficient=0.44, *P*=.08, n=18).

4 | DISCUSSION

In the present work, we show that time production in the PI task for intervals between 3 and 12 seconds is affected in subjects with HD in correlation with the UHDRS. As the most compromised brain areas

in HD are the basal ganglia and the striatal MSNs,[14, 18] poor performance in the PI task could be associated with damage in these particular regions. Specifically, a well-characterized early feature of disease pathology is transcriptional dysregulation in the MSNs. One such dysregulated gene, DA receptor D2 (DRD2), shows high expression levels in MSNs of the indirect pathway (striatopallidal) of the basal ganglia, which are among the earliest to be affected in HD.[32] The importance of dopaminergic transmission through DRD2 in the striatum has been considered to be necessary for normal interval timing.[6]

Here, we report that patients with HD had a significant underestimation of real time (decreased accuracy) for long intervals (6 and 12 seconds) as compared to controls and presented decreased amplitude and higher variability (decreased precision), as seen in Figures 1 and 2. These results are in agreement with previous findings related to interval timing impairments in patients with HD.[19–23] However, we report for the first time both decreased accuracy and precision in temporal processing in these patients. Indeed, the progression of HD disease—as measured by the UHDRS—correlates with a higher deficit in temporal discrimination (Figure 1F).

As expected according to the scalar property of interval timing,[31,33] controls showed proportionality between the standard deviation of the response distribution and the target duration being timed, thus presenting a constant coefficient of variation (CV) across these intervals. However, patients did not follow the scalar property, exhibiting higher variability for the 3- and 6-second target intervals (Figure 3).

Timing is a primary aspect of movement as most acts in real life demand the production of an appropriate force-time pattern. Deficits in timing are evident in most motor abnormalities reported in HD: increased reaction time and movement time, as well as prolonged interonset latencies when performing simultaneous and sequential movements are well documented.[34] Our results from the reaction time task indicated longer times in patients with HD than controls (Figure 4A), in agreement with previous indication of slowness of movement in HD.[35] However, reaction time did not significantly correlate with UHDRS (Figure 4B). Overall, our results indicate that interval timing but not reaction time correlates with the severity of the disease, suggesting that conscious time estimation could be a marker of the progression of HD. Both interval timing and reaction time deficits in HD result from neuronal loss in the striatum and disruption of cortico-striatal circuits.[14,18,35] Although slowness of movement was present in our patients according to the reaction time task, we hypothesize that the observed impairments in the PI task in correlation with the UHDRS are not exclusively motor. Rather, they are likely a consequence of an alteration in the internal clock due to the progressive loss of MSNs in these patients. Indeed, cognitive dysfunction in patients with HD has been reported to reflect a generalized slowing in processing, or bradyphrenia,[36] which could support some of the findings of the present work. The importance of damage in the basal ganglia on time estimation has been extensively studied in patients with PD.[9] In this sense, timing dysfunction in PD is primarily due to the loss of striatal dopaminergic input. In HD, transcriptional dysregulation and further deterioration in the MSNs may explain the observed impairments in temporal accuracy and precision.

Our study presents some limitations, such as the small size of the sample that prevents performing a further division into premanifest and manifest patient subgroups. However, a selective deterioration of time estimation has been previously reported even in presymptomatic patients with HD.[20] A further cognitive evaluation, including bradyphrenia,[36] may also be important. Despite these limitations, the present study has several strengths because it establishes a UHDRS correlation that suggests a potential role of the PI task as a biomarker of HD progression. In addition, it should be noted that some of our patients were treated with low doses of neuroleptics (as stated in Methods and Table 2). Nevertheless, there were no specific effects of medication on Peak location. Moreover, the reported effects of DA antagonists on interval timing are to produce a rightward shift on Peak location,[5] whereas in this work, we report the opposite in patients with HD. Furthermore, the neuroleptic influence in the experimental motor tasks was reported to be irrelevant at the dose used.[35]

In summary, the results of the present study indicate that patients with HD present abnormalities in short-time estimation, and suggest that recordings of cognitive performance related to timing are useful measurements of the progression of movement disorder-related pathologies. Importantly, interval timing could also be an effective assessment of cognitive decline in presymptomatic carriers of HD and familiars at risk.

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CONFLICTS OF INTEREST

The authors report no disclosures or conflict of interest concerning the research related to the manuscript.

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