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The specific role of the striatum in interval timing: The Huntington's disease model

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ABSTRACT

Time processing over intervals of hundreds of milliseconds to minutes, also known as interval timing, is associated with the striatum. Huntington's disease patients (HD) with striatal degeneration have impaired interval timing, but the extent and specificity of these deficits remain unclear. Are they specific to the temporal domain, or do they extend to the spatial domain too? Do they extend to both the perception and production of interval timing? Do they appear before motor symptoms in Huntington's disease (Pre-HD)?

We addressed these issues by assessing both temporal abilities (in the seconds range) and spatial abilities (in the cm range) in 20 Pre-HD, 25 HD patients, and 25 healthy Controls, in discrimination, bisection and production paradigms. In addition, all participants completed a questionnaire assessing temporal and spatial disorientation in daily life, and the gene carriers (i.e., HD and Pre-HD participants) underwent structural brain MRI.

Overall, HD patients were more impaired in the temporal than in the spatial domain in the behavioral tasks, and expressed a greater disorientation in the temporal domain in the daily life questionnaire. In contrast, Pre-HD participants showed no sign of a specific temporal deficit. Furthermore, MRI analyses indicated that performances in the temporal discrimination task were associated with a larger striatal grey matter volume in the striatum in gene carriers.

Altogether, behavioral, brain imaging and questionnaire data support the hypothesis that the striatum is a specific component of interval timing processes. Evaluations of temporal disorientation and interval timing processing could be used as clinical tools for HD patients.

1. Introduction

Time processing is fundamental for survival and goal achievement in humans. The question of how time is perceived becomes even more fascinating given the absence of any sensory organ or transducers dedicated to time per se, unlike the retina and its photoreceptor cells for vision for instance. Time perception operates over multiple time scales and is supported by various evolutionary biological mechanisms (Bradshaw & Szabadi, 1997). In particular, one can distinguish three relevant time scales: circadian rhythms operating over the 24-hour light/dark cycle, durations ranging from hundreds of milliseconds to minutes which are labeled interval timing, and durations in the precise millisecond range (Buhusi & Meck, 2005). The present study focuses on interval timing as this ability has been considered as crucial for various cognitive processes, such as decision-making (Gallistel, 1990; Richelle & Lejeune, 1980), rate estimation (Brighouse, Hartcher-O'Brien & Levitan,

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2014; Gibbon & Gallistel, 2000), multiple-step arithmetic (Sohn & Carlson, 2003), and learning and memory (Gallistel & Balsam, 2014).

Many theories and models have been proposed to account for how temporal information is processed. One can distinguish between two broad views. One approach suggests that the processing of feature information in neural circuits carries temporal information an intrinsic manner. (for a recent review see: Paton & Buonomano, 2018). Another line of research emphasizes the role of dedicated circuits for temporal information. In this perspective, the idea of a dedicated internal clock was put forward early by cognitive psychologists, and is still considered nowadays (Ivry & Schlerf, 2008; Treisman, 1963), in which pulses are emitted regularly by a pacemaker and temporarily stored in an accumulator (Fraisse, 1967). At the end of the interval to be timed, the number of pulses received from the accumulator is stored in a reference memory (Treisman, 1963). In the context of a time estimation task, the response is controlled by comparing current subjective time (stored in the accumulator) and the number of pulses associated with previously reinforced clock readings in reference memory. At the neural level, temporal processing has been mediated by networks involving several brain areas such as the cerebellum (Grube et al., 2010a; Ivry & Keele, 1989; Teki, Grube, Kumar & Griffiths, 2011), pre-supplementary and supplementary motor area (Halsband, Ito, Tanji & Freund, 1993; Macar, Anton, Bonnet & Vidal, 2004; Schwartze, Rothermich & Kotz, 2012), pre-motor and prefrontal cortex (Coull, Cheng & Meck, 2011; Emmons, Lewis & Miall, 2003; Oshio, 2011; Wiener, Turkeltaub & Coslett, 2010) and basal ganglia (Grahn & McAuley 2009; Pouthas et al., 2005; Rao, Mayer & Harrington, 2001). Within this network, the role of the striatum has been emphasized, as several studies have suggested that internal clock operations are regulated by dopamine neurotransmission in the basal ganglia (Artieda, Pastor, Lacruz, & Obeso, 1992; Harrington et al., 2011; Meck, 1986). The most detailed version of this view is referred to as Striatal Beat Frequency model (SBF; Meck, Penney, & Pouthas, 2008; Oprisan & Buhusi, 2011), which suggests that distributed cortical circuits contain a population of neurons oscillating at a range of different frequencies, and that the medium spiny neurons in the dorsal striatum function as coincidence detectors capturing the beats of the cortical oscillators (Matell & Meck, 2004). Recent studies support this model with neuronal data in rodents (Emmons et al, 2017; Emmons, Kennedy, Kim & Narayanan, 2019; Emmons et al, 2020). In this SBF model the input of striatal neurons is regulated by dopamine (Allman & Meck, 2012; Buhusi & Meck, 2005; Oprisan & Buhusi, 2011, 2014).

The role of the striatum in temporal processing has been mostly investigated in patients with Parkinson's disease (PD; Allman & Meck, 2012). However, PD is not primarily associated with a degeneration of the striatum but with a general loss of dopamine, which is a key input to the striatum (Kish, Shannak, & Hornykiewicz, 1988). Studies of PD support the notion that dopaminergic input regulates the speed of the internal clock, but it has no effect on the precision of temporal discrimination judgments (Artieda et al., 1992; Harrington et al., 1998; Jones et al., 2008; Pastor et al., 1992). The critical role of dopamine is further demonstrated by studies showing that blockade or increases in dopamine affect the speed of the internal clock in rats and humans (Buhusi & Meck, 2002; Cheng, Hakak & Meck, 2007; Coull, Cheng & Meck, 2011; MacDonald & Meck, 2005).

Taking these studies together, Huntington's disease (HD) may be a better model for assessing the role of the striatum in time processing, because it causes prominent cell loss with atrophy in the caudate and putamen, affecting the striatal medium spiny neurons (Graveland, Williams, & DiFiglia, 1985; McColgan et al., 2017; Vonsattel and DiFiglia, 1998). Furthermore, its diagnosis is unequivocal since HD is inherited through the autosomal dominant transmission of an expansion of the trinucleotide CAG-repeats within the huntingtin gene on the short arm of chromosome 4. This genetic diagnosis also makes it possible to test individuals at the pre-manifested stage of HD (hereafter Pre-HD) carrying the huntingtin mutation but not yet exhibiting the motor symptoms associated with HD. Importantly, such Pre-HD participants exhibit a specific neural atrophy affecting the striatum (Tabrizi et al., 2013).

At the clinical level, HD patients display motor (chorea, dystonia, and gait disturbances), behavioral (mostly depression and anxiety) and cognitive deficits (affecting executive functions in particular). Disease onset, as defined by the motor symptoms, typically occurs in mid-life. Patients may however display cognitive and behavioral disorders much earlier. Among those, HD patients often report difficulties with temporal processing in their daily life, and a variety of laboratory tasks have confirmed that HD patients are impaired relative to Controls (Agostino et al., 2017; Beste et al., 2007; Cope, Grube, Singh, Burn & Griffiths, 2014; Paulsen et al., 2004; Rao, Marder, Uddin, & Rakitin, 2014; Righi et al., 2016). Whether the deficit in temporal processing extends to Pre-HD individuals is unclear. Some studies reported a deficit in Pre-HD patients relative to age-matched Controls in time perception (Paulsen et al., 2004) and production (Beste et al., 2007; A. K. Rao et al., 2014), whereas other studies found no deficit in perception (Beste et al., 2007). Furthermore, Pre-HD individuals do not typically complain about temporal disorders in daily life; these therefore remain to be confirmed.

Another question that has not been fully addressed regarding the temporal deficit documented in previous studies is whether it is specific to the temporal domain, or whether it might reflect a more general impairment not specifically associated with temporal processing *per se*. In other words, one possibility is that gene carriers (i.e., HD patients and Pre-HD individuals) exhibit specific difficulties with time, consistent with the hypothesis of an internal clock centralized and located in the striatum, whereas another possibility is that they might suffer from a domain-general impairment. This domain-general impairment would be also consistent with the known cognitive and motor deficits of HD patients. Yet, past studies have typically compared performances of gene carriers and controls only in the temporal domain, without using a control task to assess the specificity of this temporal deficit. One exception is the study of Paulsen et al. (2004) who used pitch discrimination as a control task, but this study did not report the comparison between the temporal and the control tasks for gene carriers, nor the interaction between tasks (temporal vs. control) and groups (controls vs. gene carriers). In other words, the specificity of the deficit in temporal processing in gene carriers remains to be established.

To address this question, in our study we chose space as a control domain, and tested gene carriers and healthy participants in behavioral tasks aimed at measuring both their spatial and temporal abilities. This choice of space as a comparison domain was guided by several reasons. Both space and time involve a continuous metric, and tasks testing temporal processing can be easily translated into the spatial domain at the same level of complexity. Furthermore, past studies have found functional similarities between space and time: both systems interact with numerosity estimations (Cappelletti, Freeman & Cipolotti, 2009), and time can be represented using space (e.g. mental time line, Di Bono et al., 2012). Pastor et al. (2004) even reported the activation of basal ganglia by discrimination tasks in both domains.

In the present study, we thus compared temporal processing (in the seconds range) and spatial processing (in the centimeters range) in HD patients, Pre-HD and healthy participants (Controls), using similar paradigms for the two domains. To test the hypothesis of a centralized disorder of the internal clock located in the striatum, we tested temporal processing in both perception and production. A central clock deficit must involve both perception and production modalities, whereas an access or output deficit may only involve one or the other. We additionally measured participants' temporal and spatial difficulty in their daily life through a self-completed questionnaire. Finally, we assessed whether the behavioral results correlated with the striatal atrophy measured with voxel-based morphometry (VBM), and whether they translate to daily life impairments as measured by a specific questionnaire.

2. Materials and methods

2.1. Participants

Forty-five carriers of the Huntingtin (Htt) gene (CAG repeats > 35), including 20 Pre-HD (Total Functional Capacity scores = 13 and Total Motor Scores of Unified Huntington Disease Rating Scale ≤ 5), 25 HD patients at an early stage of the disease (stage I, according to their Total Functional Capacity scores; Shoulson, 1981) and 25 healthy participants (Controls) were enrolled in the study. The burden score, an index of disease burden, was calculated from a formula (age × [CAG–35·5]) (Penney, Vonsattel, Macdonald, Gusella, & Myers, 1997). We estimated the predicted age at motor onset (estimated onset) by using a survival analysis regression equation based on CAG repeat length (Langbehn et al., 2004). We then subdivided Pre-HD participants into two groups based on whether they were far (Pre-HD Far) or close (Pre-HD Close) to the estimated onset of the disease (median split at 6.6 years from onset). All groups were matched for age, years of education, sex and handedness (pairwise comparisons between any two groups, for each of these variables: all $p > .05$; see Table 1 for the demographic data). They were recruited from an out-clinic study of "predictive biomarkers in HD" (NCT01412125) approved by the local ethics committee of Henri Mondor Hospital (Créteil, France). None of the participants had any history of neurological or psychiatric disorders other than HD. All gave written informed consent before participation in the study.

2.2. Clinical assessment

Gene carrier participants were evaluated with the Unified Huntington's Disease Rating Scale (UHDRS, Kieburtz et al., 2001) and the Mattis Dementia Rating Scale (MDRS; Mattis, 1976). The data are summarized in Table 2. Groups of Pre-HD Close and Pre-HD Far were matched for all clinical performance (all $p > .05$).

2.3. Behavioral tasks

Participants performed six tasks assessing their perception and production abilities in both the temporal and spatial domains. For each domain, they were asked to perform a bisection task (administration time: 5 min), a discrimination task (administration time: 15 min), and a production task (administration time: 5 min). They were also asked to complete a questionnaire evaluating temporal and spatial disorientation in daily life (administration time: 3 min). The entire assessment took<60 min. A schematic diagram of the tasks is presented in Fig. 1. Half the participants began with the temporal domain tasks and the other half began with the spatial domain tasks. Stimuli were presented on a laptop with a 15.4-inch screen, using E-prime2.0 software (http://www.pstnet.com/eprime.cfm). Participants were seated 50 cm from the screen.

Table 1
Demographic data for Pre-HD participants, HD patients and Controls. Participants in the Pre-HD group were divided into Close from onset and Far from onset based on estimated onset.

	Pre-HD	Pre-HD Close	Pre-HD Far	HD	Controls
Number of participants	20	10	10	25	25
Sex	8 M/12F	5 M/5F	3 M/7F	14 M/11F	10 M/15F
Age (years)	44.1 ± 9.3	47 ± 8.9	41.1 ± 9.1	49 ± 9.2	46.2 ± 7.7
Years of education	13.4 ± 2.9	13.8 ± 3.2	13 ± 2.7	13.1 ± 2.8	14 ± 2.9
Handeness	18R/2L	9R/1L	9R/1L	22R/3L	21R/4L
Disease duration	_	_	_	5.2 ± 5.8	_
CAG repeats	42.7 ± 2.5	43.6 ± 2.9	41.7 ± 1.5	44.4 ± 2.7	_
Estimated onset	6.9 ± 8.6	0.8 ± 5.9	13.2 ± 6.1	_	_
Disease burden score[a]	303.1 ± 86.3	360.5 ± 82.3	245.8 ± 40.6	417.2 ± 74.6	_

F = female, M = male, R = right-handed, L = left-handed.
[a]Disease-burden score = age × (CAG length – 35.5), Penney, Vonsattel, MacDonald, Gusella, and Myers (1997).

Table 2
Clinical performance of Pre-HD and HD patients.

	Pre-HD	HD	p values	Normal values
Total functional capacity (TFC)	13 ± 0	11.9 ± 0.8	< .001	13
UHDRS_TMS[a]	0.35 ± 0.9	23.8 ± 12.2	< .001	0
Mattis Dementia Rating Scale	139.9 ± 5.4	134.6 ± 7	.007	> 136[b]
Stroop color/word	47.3 ± 11.1	31.5 ± 11.5	< .001	> 35[c]
Fluency for PRV (in 2 min)	63 ± 22.8	38.2 ± 17	.002	> 45[d]
Symbol digit test modality	49.9 ± 13.4	31.7 ± 8.6	< .001	46.8 ± 8.4[e]

[a]UHDRS_TMS = United Huntington Disease Rating Scale, Huntington Study Group_Total Motor Score (1996).
* Normal values obtained from: [b] Mattis (1976), [c] Golden and Freshwater (1978), [d]Cardebat et al. (1990), [e]Centofanti (1975).

2.3.1. Bisection paradigm

Bisection was evaluated by training participants with two references, corresponding to short or long values, and then presenting a series of intermediate values and asking the participants to determine whether they were closer to the short or the long reference, by pressing the corresponding key on the computer keyboard (right index finger for "long", left index finger for "short"). Stimuli were repeated eight times and displayed at random, resulting in 72 trials without feedback (9 intermediate values × 8 times). A training phase of 16 trials with feedback preceded the test phase. Our a priori inclusion criterion was that participants who made more than two mistakes during the training phase would not continue to the main test phase, but in practice no participants failed this criterion. The inter-trial interval was 1000 ms.

In the temporal bisection task, the stimulus was materialized as the time interval between the appearance of a central black dot against a white background, and that of a red dot within the black dot. The short reference was 300 ms, the long reference was 1800 ms, and the intermediate time intervals ranged from 450 ms to 1650 ms, with 150 ms steps.

In the spatial bisection task, the stimulus was the distance between a central black dot and a peripheral black dot against a white background on the computer screen. The short reference was 2.2 cm, the long reference was 8.2 cm, and intermediate distances from 2.8 cm to 7.6 cm, with 0.6 cm steps, were presented.

2.3.2. Discrimination paradigm

Discrimination was evaluated with a same-different task, using an AAX procedure. In each trial, participants were presented with three stimuli and asked whether the last stimulus (X) was similar to the first two (AA) or different. The response was delivered by pressing the corresponding key on the computer keyboard (right index finger for "same" or left index finger for "different"). The stimulus of reference "A" could be either short (S) or long (L), resulting in an SSX or an LLX task. Stimuli were repeated six times and displayed at random, resulting in 108 trials without feedback: (2 references: S and L) × (9 "X") × (6 times). A training phase of six trials with feedback preceded the test phase. The inter-trial interval was 1000 ms.

In the temporal discrimination task, the duration stimulus was materialized as a central black dot against a white background on the

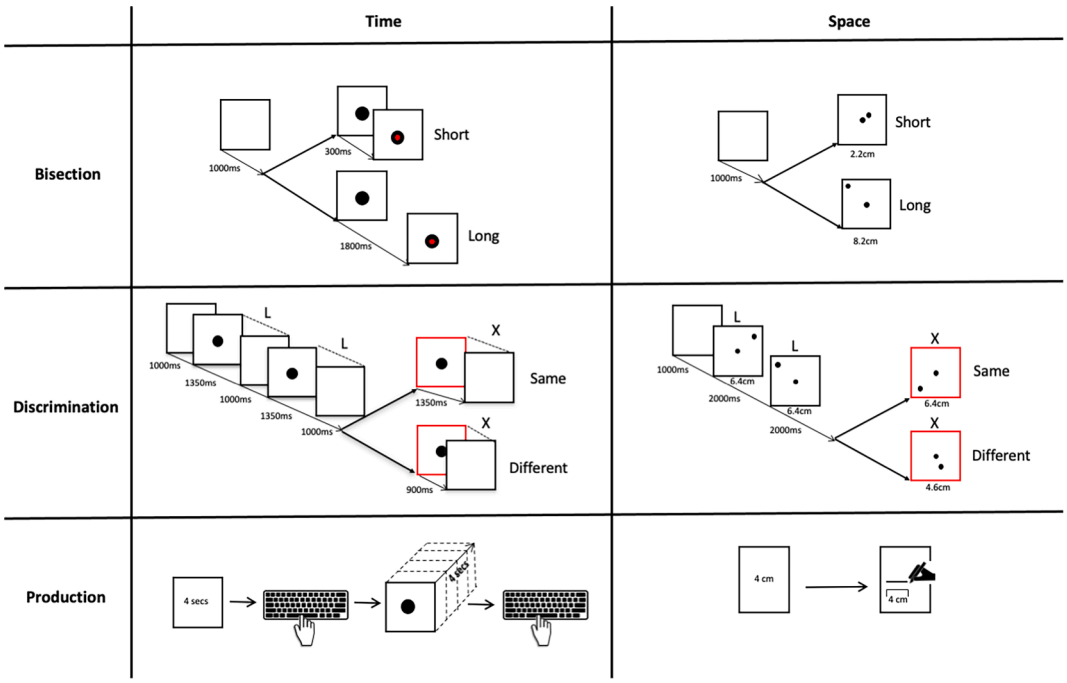

Fig. 1. Schematic illustration of the four paradigms assessing temporal and spatial processing. In the bisection tasks, participants have to indicate whether a given duration or spatial distance corresponds to a short or a long reference, to which they have been previously exposed. In the discrimination tasks, participants receive three stimuli and have to judge whether the third one is the same as the first two. In the production tasks, participants are asked to press the spacebar for a given duration or to draw a line with a given length.

computer screen. The short reference (S) was a stimulus lasting 750 ms, whereas the long reference (L) lasted 1350 ms. X took values from 150 ms to 1350 ms, in 150 ms steps, relative to S, and from 750 ms to 1950 ms, with 150 ms steps, relative to L.

In the spatial discrimination task, the stimulus was materialized as the distance between a central and a peripheral black dot against a white background on the computer screen. The short reference (S) was 4 cm and the long reference (L) was 6.4 cm. X could take values from 1.6 cm to 6.4 cm, with 0.6 cm steps, for comparison with S, and from 4 cm to 8.8 cm, with 0.6 cm steps, for comparison with L. In half the trials, the peripheral dot moved in a clockwise direction, whereas, in the other half, it moved counterclockwise, with a 90° rotation around the central dot between the first and second A, and a rotation of 135° to 180° between the second A and X. Each stimulus was presented for 2000 ms.

2.3.3. Production paradigm

The participants were presented with numerical values and were asked to produce the corresponding distance or duration. Stimuli were repeated three times and displayed in a fixed order, resulting in 21 trials without feedback (7 values × 3 times). A training phase of two trials preceded the test phase.

In the temporal production task, a black dot appeared in response to the participant pressing on the spacebar. Participants were asked to press the spacebar again when they considered that dot had been on the screen for the duration previously indicated. Durations of 4 to 10 s, with one-second steps, were presented.

In the spatial production task, a value in centimeters was presented on an A4 sheet. The participants were asked to draw a line of the length indicated manually on the sheet of paper. Distances of 4 to 10 cm, with 1 cm steps, were presented. Because we found in pilot studies on healthy participants that articulatory suppression did not impact performance in this task, we removed articulatory suppression from the present paradigm, to avoid creating non-specific impairments related to dual tasking (Delval et al., 2008).

2.3.4. Questionnaire

We designed a novel questionnaire including 10 questions about the temporal domain (e.g. Have you been using your calendar more frequently lately?) and 10 questions about the spatial domain (e.g. Do you hesitate to go to unknown places alone?). The questions from the two domains were matched for sentence length ($F < 1$). They assessed temporal or spatial disorientation, rather than specific insight into time or space processing. To ensure the specificity of the questionnaire, items for which>20% of "disoriented" responses were obtained in Controls were eliminated. Then, an expert in Huntington's disease, not familiar with the questionnaire, suggested the removal of 5 questions per domain, on criteria of homogeneity and sensitivity. A second person, not familiar with questionnaire, calculated Cronbach's coefficient alpha ($\propto > 0.5$)with and without the questions suggested by the expert, so as to retain 5 questions per domain in the final analysis. The final list of questions is presented in Supplementary Material (section Questionnaire).

2.4. MRI scanning

Twenty-four HD patients and 17 Pre-HD participants underwent structural brain MRI within a six-month window around the behavioral evaluation. Brain atrophy was assessed by comparing their MRI scans with an external reference cohort (without behavioral testing) of 24 healthy volunteers matched for age (47.8 ± 10.5, Pre-HD*healthy p = 0.21, HD*healthy p = 0.72) and sex (10 M/14F, Pre-HD*healthy p = 0.98, HD*healthy p = 0.40). MRI was performed at Henri Mondor Hospital (Créteil, France), on a Siemens Symphony 1.5 T MRI scanner with a 12-channel head coil. For 20 HD patients, 14 Pre-HD participants and 24 healthy volunteers MRI included a T1-weighted magnetization-prepared rapid gradient-echo acquisition (MP-RAGE, TE/TR = 3.72/2400 ms, TI = 1000 ms, flip angle = 8°, acquisition matrix = 256 × 256, FOV = 256 × 256 mm, voxel size = 1 × 1 × 1 mm3, sagittal sections: 160). For 4 HD patients and 3 Pre-HD participants MRI included a T1-weighted MP-RAGE with different parameters (TE/TR = 2.26/2300 ms, TI = 900 ms, flip angle = 9°, acquisition matrix = 256 × 256, FOV =

256 × 256 mm, voxel size = 1 × 1 × 1 mm3, sagittal sections: 192).

2.5. Behavioral analysis

For each behavioral task and each participant, we considered the psychometric curve that related participants' responses to the various levels of the stimuli. Psychometric curves were fitted separately for each individual and task, as detailed below for each task (see Fig. 2 for an example). Psychometric fits were achieved with Matlab (https://www.mathworks.com/), and statistical tests were performed in R (https://www.r-project.org/). From these fits, we used the parameter σ, as our variable of interest to evaluate performance. Specifically, this parameter σ quantifies how much a participant's responses are insensitive to the stimulus feature relevant for the task. The larger the value of σ, the more the participant is answering at random in the task.

2.5.1. Bisection paradigm

In the bisection paradigm, we fitted a cumulative Gaussian curve to our behavioral data, as described by Eq. (1) below. The psychometric curve relates the probability of identifying the stimulus as long, denoted $P(\text{'long'})$, for the stimulus value presented in each trial, denoted x. The parameter σ quantifies the noise in the perceptual decision process. More specifically, it scales with the inverse of the maximum slope of the psychometric curve.

$$P('long') = \Phi\left(\frac{x-c}{\sigma}\right) \tag{1}$$

A large number of participants displayed a near-chance level of performance for the data point furthest to the left (condition $x = 450$ ms in the temporal task; condition $x = 2.8$ cm in the spatial task). We therefore excluded this point during the fitting procedure, for all conditions and participants to increase the quality of the fit and better capture the data.

2.5.2. Discrimination paradigm

For the discrimination paradigm, we fitted to the experimental data a psychometric curve relating the probability of identifying the stimuli as identical, noted $P(\text{'same'})$, to the value × of the stimulus difference in the trial. We used Eq. (2) below, in which Φ is the cumulative of the standard normal distribution, c_1 and c_2 are criterion parameters (capturing the general bias towards responding 'same' during the task), and σ is the noise in the discrimination process (here again, it scales with the inverse of the maximum slope of the psychometric curve).

$$P('same') = \Phi\left(\frac{x+c_1}{\sigma}\right) - \Phi\left(\frac{x-c_2}{\sigma}\right) \tag{2}$$

In the spatial task, the two criteria (c_1; c_2) were assumed to be equal, whereas, for the temporal task, they were allowed to differ, as visual inspection of the data revealed that this approach was more appropriate.

The parameter of interest in our analyses (σ) quantifies perceptual ability in the task. We fitted separate curves for each participant and reference (short vs. long), and then looked at how σ was affected by group (Controls, Pre-HD, HD) and reference (short vs. long).

We also analyzed the overall frequency of 'same' responses in each individual, as a measure of bias (see Supplementary Material).

2.5.3. Production paradigm

For the production paradigm, we fitted a linear regression to predict the duration or distance produced from the duration or distance requested, as described in Eq. (3).

$$Y = ax + b + \varepsilon,\ \varepsilon \sim N(0, \sigma^2) \tag{3}$$

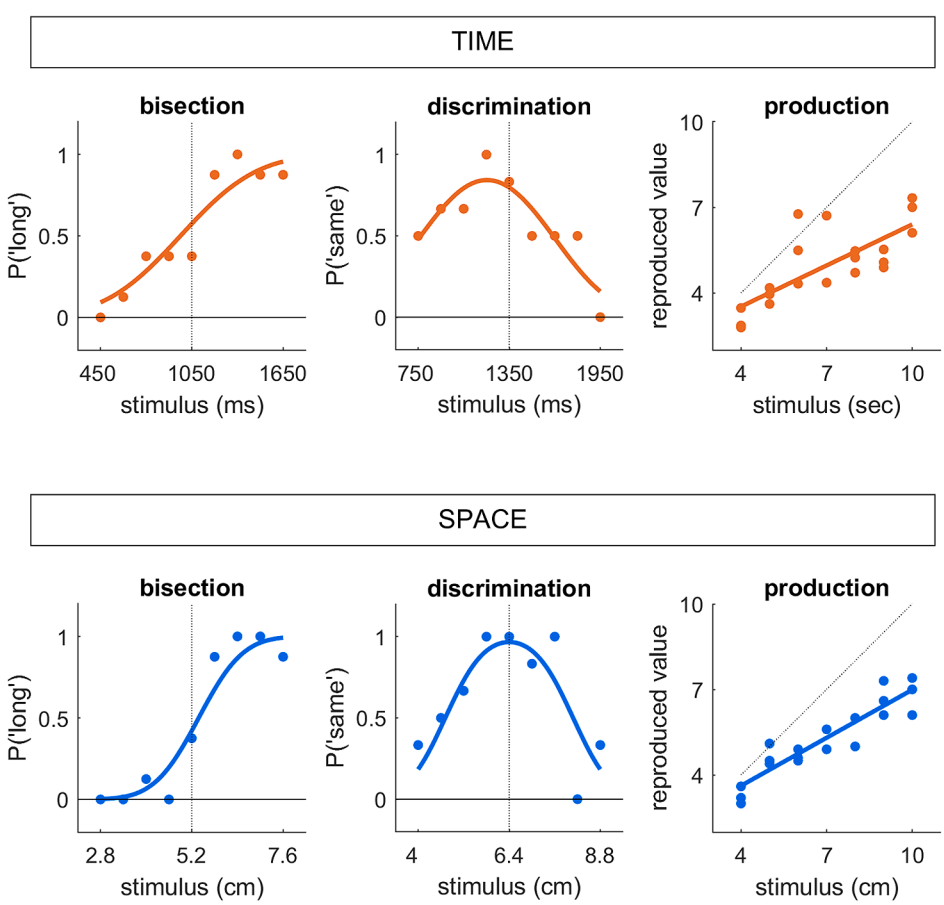

Fig. 2. Illustration of the psychometric curves for behavioral performance. Behavioral performance for one HD patient in the temporal tasks (top row) and spatial tasks (bottom row). Lines are fitted psychometric curves (see methods). For the discrimination (left panels) and bisection (middle panels) tasks, the dots represent the probability of the binary response within each of the nine stimulus conditions, and the parameter of interest, σ, corresponds to the inverse of the maximum slope of the fitted curves. For the discrimination panel, only the long reference is presented. For the production task (right panels), the dots correspond to individual trials, and the parameter of interest σ corresponds to the jitter (along the y-axis) of the dots relative to the best-fit line.

This regression includes a slope parameter (a) and an intercept parameter (b), and enabled us to evaluate performance as the standard deviation of the residual error (σ). This value quantifies the noise in the production responses, that is, the variation of a participant's productions for a given stimulus level.

2.5.4. Questionnaire

The response to each question was scored "0″ for a negative answer or "1" for a positive answer indicating disorientation. The score for each participant was the mean score across the 5 questions per domain. Higher scores indicate higher levels of temporal/spatial disorientation in daily life.

2.5.5. Outlier correction

As values of σ may diverge towards infinity when participants approach chance performance, we applied winsorizing (Tukey, 1962) as an outlier correction to limit the impact of extreme data points. More precisely, values of σ were capped at the 0.75 quantile plus 4 times the interquartile range, across all participants, separately for each task and each domain. Supplementary Figure A illustrates the raw data and the corresponding cutoff point in the winsorizing procedure, and Supplementary Table A indicates the number of data points affected, as well as their initial and corrected values.

2.5.6. Group level statistics

For each paradigm (bisection, discrimination, production, and questionnaire), we performed analyses of variance (ANOVAs) with group (Controls, Pre-HD, and HD), domain (temporal vs. spatial) and their interaction, as independent factors. We ran additional ANOVAs within each domain, to evaluate group effects and pairwise comparisons of groups. We included age as a covariate in all these analyses. Effect sizes calculated as omega-squared (ω^2) (for small sample sizes, ω2 reduces bias; Lakens, 2013) and reported only for $F > 1$. We considered 0.01, 0.06, 0.14 as small, medium and large effect sizes, respectively (Kirk, 1996). Finally, we evaluated the correlation between performances for the different behavioral tasks together and the relationship between behavioral performance and the results of clinical assessment tests, and demographic data, with Pearson's correlation analyses.

2.6. MRI data analysis

2.6.1. Preprocessing

VBM data preprocessing and analysis were performed with CAT12 (*www.neuro.uni-jena.de/cat/*), an SPM12 toolbox (*http://www.fil.ion.ucl.ac.uk/spm*) running on Matlab. Structural images were corrected for intensity bias, classified by tissue and registered, by linear and non-linear transformations (DARTEL) within a unified model (Ashburner & Friston, 2005). Grey matter segments for each participant were modulated with non-linear components of the normalization only, thereby preserving actual tissue values locally, making it possible to take individual brain size into account globally. Modulated, normalized grey matter segments were smoothed with a 6 mm FWHM Gaussian kernel.

2.6.2. Group level statistics

VBM analyses investigated regional differences between gene carrier participants (HD and Pre-HD) and Controls in terms of smoothed, modulated and normalized grey matter volume and delineated grey matter atrophy. Our approach was similar to a previous study looking at correlations between VBM and linguistic performance in HD patients (Giavazzi et al., 2018). We first assessed group differences (Controls vs. gene carriers) in grey matter volume with a full factorial design model, with group as the main factor and age, total intracranial volume (TIV) and the type of MRI sequence used as covariates. An atrophy mask was created by pooling the clusters observed using family-wise error correction (FWE-corrected, $p < .05$) for multiple comparisons with a threshold of at least 50 contiguous voxels. This atrophy mask represented the areas of grey matter atrophy in gene carriers relative to controls. This atrophy mask was used for subsequent analyses of the correlation with behavioral data. Significant clusters were anatomically labeled by superimposing the statistical parametric maps on the AAL atlas implemented in MRIcron software (*http://www.mricro.org*).

We then conducted a series of multiple regression analyses to explore the correlations between performance in each behavioral task and the grey matter volume in the 41 gene carrier participants. For each separate model, age, TIV and MRI type was used as covariates. Statistical analysis was explicitly constrained within the atrophy mask created in the between-group comparison and proportional scaling was used for normalization. Statistical outcomes were observed with corrected p-values inferior to 0.05 using Family-Wise Error (FWE) and a minimum of 50 voxels per cluster. For each gene carrier participant, we extracted the mean probability of GM values within the significant clusters. Pearson correlation tests were then performed to determine the strength of the relationship between GM values and behavioral performances.

3. Results

3.1. Behavioral tasks

Figs. 3 and 4 illustrate the performance in the 3 behavioral tasks and the questionnaire score, and Table 3 summarizes our behavioral results.

3.1.1. Bisection paradigm

The group × domain ANOVA indicated a main effect of group ($F(2.67) = 9.15$, p=<.001, $\omega^2 = 0.09$) and domain ($F(1.67) = 61.79$, $p < .001$, $\omega^2 = 0.23$) with a significant group × domain interaction ($F(2.67) = 6.37$, $p = .002$, $\omega^2 = 0.04$), related to a specific deficit for HD patients in the temporal domain as detailed below (see also Fig. 4 and Table 3). Indeed, when restricting this ANOVA to HD patients vs. Controls, the group effect ($F(1.48) = 14.12$, $p < .001$, $\omega^2 = 0.1$) and the group × domain interaction ($F(1.48) = 7.06$, $p = .01$, $\omega^2 = 0.03$) remained significant, but this was not the case when restricting the analysis to Pre-HD vs. Controls (both $p > .2$).

When focusing on the temporal task, a main effect of group was found (($F(2.67) = 9.52$, $p < .001$, $\omega^2 = 0.19$), and pairwise comparisons confirmed that HD patients performed worse than Controls, or Pre-HD , without difference between Controls and Pre-HD (see Table 3). In the spatial domain, by contrast, no main effect of group was found ($p = .07$), but for completeness we conducted pairwise comparisons, which showed a difference between HD patients and Controls, and no difference between the other groups

3.1.2. Discrimination paradigm

An ANOVA with group, domain and reference as independent variables indicated main effects of group ($F(2,67) = 28.01$, $p < .001$, $\omega^2 = 0.18$) and domain ($F(1,67) = 46.02$, $p < .001$, $\omega^2 = 0.13$), with a significant group × domain interaction ($F(2,67) = 15.21$, $p < .001$, $\omega^2 = 0.08$). Besides, Participants performed better with short than with long references ($F(1,67) = 52.41$, $p < .001$, $\omega^2 = 0.04$), consistently with Weber's law. Significant reference × domain ($F(1,67) = 11.74$, $p < .001$, $\omega^2 = 0.01$) and reference × group interactions ($F(2,67) = 8.70$, $p < .001$, $\omega^2 = 0.01$) were also found. In brief, HD and Pre-HD patients were globally impaired relative to Controls, but for HD patients the deficit was more pronounced in the temporal domain than in the spatial domain. Indeed, when restricting the ANOVA to HD patients vs. Controls, the group effect (F=(1,48) = 44.04, $p < .001$, $\omega^2 = 0.19$) and the group × domain interaction (F=(1,48) = 23.3, $p < .001$, $\omega^2 = 0.08$) remained significant, whereas when restricting the analysis to Pre-HD vs. Controls only the group effect remained significant (F=(1,48) = 8.65, $p < .005$, $\omega^2 = 0.05$).

When analyzed separately, the temporal discrimination task showed a main effect of group ($F(2,67) = 22.82$, $p < .001$; $\omega^2 = 0.30$), together with a main effect of reference ($F(1,67) = 29.71$, $p < .001$, $\omega^2 = 0.05$)

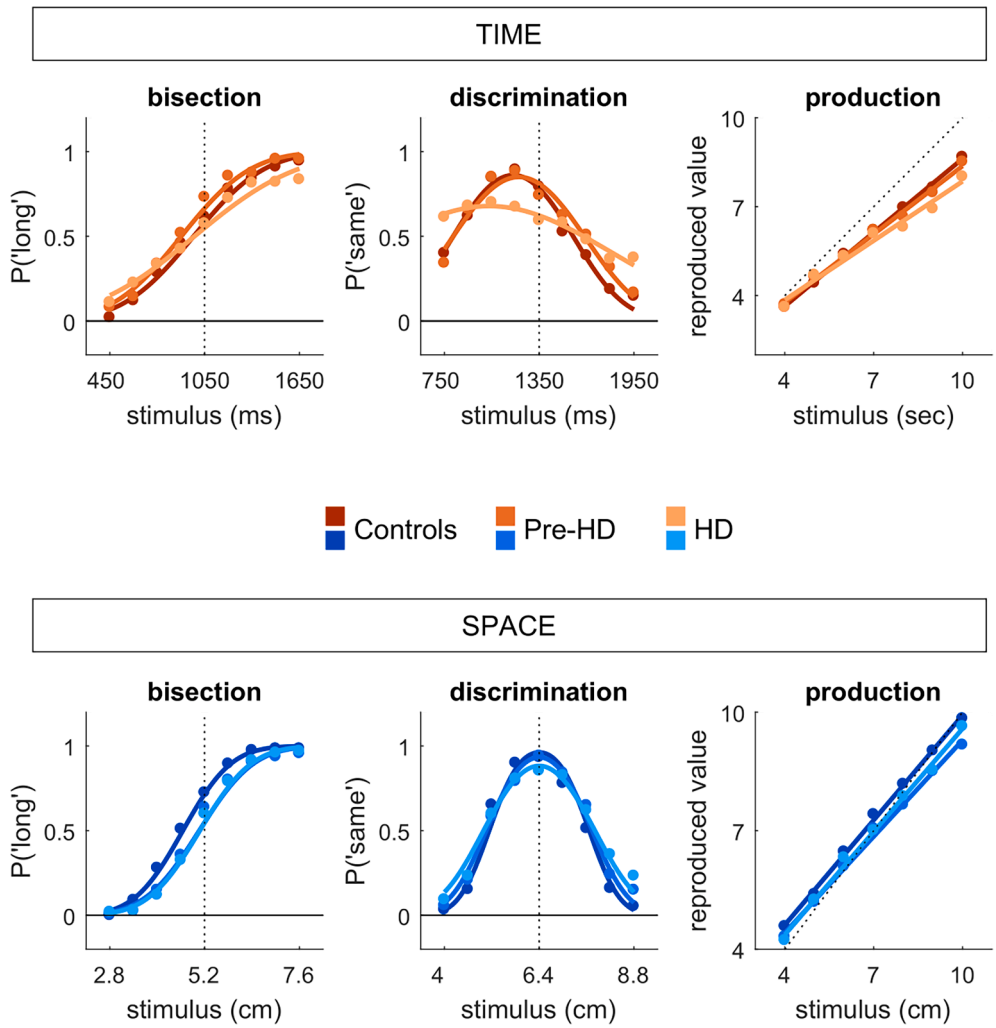

Fig. 3. Group-level psychometric curves. Each panel corresponds to a particular behavioral task and domain (temporal vs. spatial). In each panel, dots represent the average response across participants, separately for each group (Controls, Pre-HD, HD). For illustration purposes, we also represented with a line the fit of this aggregate response, using the same psychometric function as used at the individual level.

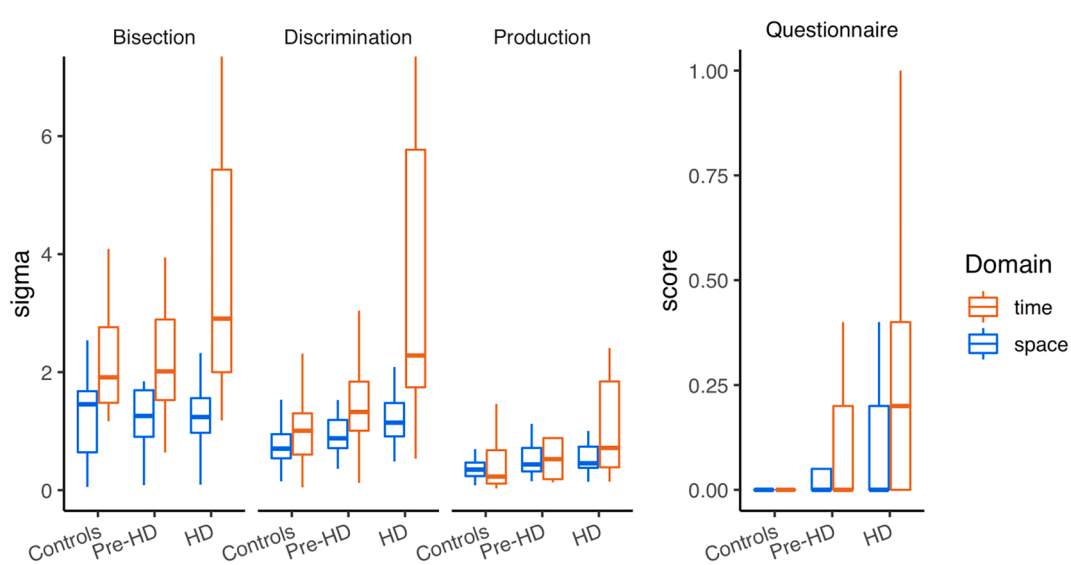

Fig. 4. Behavioral results. Performance measures (σ parameter for the behavioral tasks and scores for the questionnaire) aggregated for each group, within each task and domain (spatial vs. temporal). Lower scores correspond to better performances. The boxes and hinges represent the median, first quartile (Q1), and third quartile (Q3). The two lines extend each boxplot to 1.5 times the interquartile range above and below these quartiles.

Table 3
Summary of the results on behavioral tasks.

	Group × domain interactions				Group effects for Time				Group effects for Space			
	All groups	HD vs Controls	Pre-HD vs HD	Pre-HD vs Controls	All groups	HD vs Controls	Pre-HD vs HD	Pre-HD vs Controls	All groups	HD vs Controls	Pre-HD vs HD	Pre-HD vs Controls
Bisection	**	*	**	n.s.	***	***	**	n.s.	n.s.	*	n.s.	n.s.
Discrimination	***	***	**	n.s.	***	***	***	*	***	***	*	*
Production	n.s.	n.s.	n.s.	n.s.	n.s.	*[1]	n.s.[1]	n.s.[1]	n.s.	n.s.[1]	n.s.[1]	n.s.[1]
Questionnaire	+	n.s.	*	n.s.	**	**	+	n.s.	n.s.	n.s.	n.s.	n.s.

n.s. = non-significant *($p > .1$) ;* $+p < .1$; $*p < 0.05$; $**p < 0.01$; $***p < 0.001$
[1] note that given the absence of a group × domain interaction in the production task, the comparisons between groups for each domain should be taken with caution.

and a group × reference interaction (F(2,67) = 8.97, $p < .001$, $\omega^2 = 0.03$), and pairwise comparisons were all significant (Table 3), with HD patients performing worse than Pre-HD who in turn, performed worse than Controls. The spatial discrimination task showed a (weaker) main effect of group (F(2,67) = 12.37, $p < .001$, $\omega^2 = 0.19$) and a (stronger) main effect of reference (F(1,67) = 51.38, $p < .001$, $\omega^2 = 0.1$), without interaction ($p = .5$). As for time, pairwise comparisons indicated that HD patients performed worse than Pre-HD participants, who in turn performed worse than Controls.

3.1.3. Production paradigm

The group × domain ANOVA indicated main effects of group (F (2,67) = 3.4, $p = .039$, $\omega^2 = 0.03$), and domain (F(1,67) = 7.26, $p = .009$, $\omega^2 = 0.05$), without interaction ($p = .37$). The group effect was still present when restricting this analysis to HD patients vs. Control (F= (1,48) = 6.74, $p = .013$, $\omega^2 = 0.05$) but not when focusing on Pre-HD vs. Controls ($p > .1$). The group × domain interaction was not present in either case ($p > .2$). Overall, thus, HD patients performed worse than Control participants, but we found no evidence that this deficit would be specific to the temporal domain.

In the temporal domain, the main effect of group was not significant ($p = .12$) and pairwise comparisons revealed only one significant difference, by which HD patients performed less well than Controls in the temporal domain. However, given the absence of a group × domain interaction, these results should be taken cautiously. In the spatial domain, we found no main effect of group ($p = .28$) and no pairwise differences.

3.1.4. Daily life questionnaire

An ANOVA on the questionnaire responses indicated a main effect of group (F(2,67) = 5.84, $p = .005$, $\omega^2 = 0.07$), and domain (F(1,67) = 6.16, $p = .02$, $\omega^2 = 0.03$) with a group × domain interaction (F(2,67) = 3.07, $p = .05$, $\omega^2 = 0.02$). When this analysis was restricted to HD patients, both the main effect of group (F (1,48) = 9.01, $p = .004$, $\omega^2 = 0.09$) and the group × domain interaction (F=(1,48) = 6.14, $p = .017$, $\omega^2 = 0.03$) remained significant, but this was not the case when focusing on Pre-HD vs. Controls (both $p > .05$). Overall, the data indicated a greater disorientation reported by HD patients than by Controls, but only in the temporal domain.

When examining the temporal questionnaire, the group effect was significant ($p = .001$) and pairwise comparisons indicated a higher degree of temporal disorientation for HD patients than Controls, or HD patients, without difference between Pre-HD patients and Controls. For the spatial domain, no main effect of group was found, and no difference was found in pairwise comparisons (all $p > .05$).

3.1.5. Examining Pre-HD close and far from estimated onset

In order to detect behavioral signs before the onset of motor symptoms, following previous studies, we also examined more precisely Pre-HD participants, as a function of whether they are estimated to be close (Pre-HD Close) or far (Pre-HD Far) from the onset of the symptoms. Overall, we found the same results when comparing Controls to the whole group of Pre-HD participants (see Table 3), and when comparing Controls to either Pre-HD Far or Pre-HD Close participants. That is, both Pre-HD Close and Pre-HD Far participants were worse than Controls in the discrimination paradigm, with no evidence of a specific deficit for the temporal domain. The only exception was in the case of the bisection task, where the comparison between Pre-HD Far and Controls indicated a group × domain interaction (F(1, 33) = 4.64, p = .039), however the group effect was not significant when estimated in the temporal and spatial domain (both p > .125).

Finally, we directly compared Pre-HD Far to Pre-HD Close participants. Here, we found a significant group × domain interaction in the bisection task (F(1, 18) = 5.35, p = .033), where Pre-HD Close were worse than Pre-HD Far participants, in the temporal domain (F(1, 18) = 8.03, p = .012) but not in the spatial domain (p = .989). No significant main effect or interaction was found in the other tasks in this comparison.

3.1.6. Correlation analyses

Across all participants, performances were overall correlated amongst temporal tasks, but less so amongst spatial tasks (Table 4). This suggests that the source of variation for performance is shared amongst temporal but less so amongst spatial tasks. One other aspect that is noticeable is the relatively good correlation between the bisection and discrimination tasks, even across domains. This may be due to similar demands in terms of procedure between these two tasks. We have checked scatterplots visually to ensure that the correlations were not driven by outliers, and conducted additional analyses showing that these correlations were not simply due to group membership (Supplementary Figure B).

Correlations between tasks and clinical scores in gene carriers (Pre-HD and HD patients; Table 5), showed that the disease burden score as well as most clinical scores (TFC, UHDRS_TMS, MDRS, Stroop, SDMT) were correlated with the discrimination and bisection tasks in the temporal domain. In the spatial domain however, clinical scores were only correlated with the discrimination task. There were no correlations between behavioral performance in any task and the estimated onset in the Pre-HD group (all $p > 0.09$).

3.2. Voxel-based morphometry

Grey matter volume in gene carrier participants (Pre-HD and HD patients) was smaller than that in Controls, especially in the striatum (both left and right putamen in the voxel-based morphometry analysis; Supplementary Table B). VBM analyses were then restricted to gene carriers and to the atrophy mask obtained by comparing gene carriers with Controls (Fig. 5A). Within this mask, performance in the temporal discrimination task was positively correlated (i.e. the parameter σ was negatively correlated) with the volume of grey matter in only two clusters, one in the left putamen (MNI coordinates x,y,z = -14,10,-10; T = 5,36; $p < .05$, FWE-corrected, cluster size = 809 voxels; r = -0.58; p < .001) and one in the right caudate (MNI coordinates x,y,z = 14,14,-10; T = 4.33; $p < .05$, FWE-corrected, cluster size = 335 voxels; r = -0.55; p < .001), as illustrated in Fig. 5B. This analysis included age, TIV and MRI type as a covariate. No correlation was found between performance in

Table 4
Results of correlation analyses between behavioral tasks across all participants (N = 70).

Behavioral Tasks	Time Bisection	Discrimination	Production	Questionnaire	Space Bisection	Discrimination	Production	Questionnaire
Time								
Bisection	_	0.58***	0.29*	0.24*	0.29**	0.49***	0.05	0.13
Discrimination		_	0.38***	0.41***	0.42***	0.45***	0.10	0.17
Production			_	0.15	0.06	0.08	−0.07	0.13
Questionnaire				_	0.15	0.24	−0.01	0.25*
Space								
Bisection					_	0.38***	0.06	0.16
Discrimination						_	0.19	0.28*
Production							_	−0.01

‘’ *(p > .05)* ; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$, uncorrected

Table 5
Results of correlation analyses between behavioral tasks and demographic data and clinical performance in gene carriers (N = 45).

	Behavioral Tasks Time Bisection	Discrimination	Production	Questionnaire	Space Bisection	Discrimination	Production	Questionnaire
Demographic Data								
Sex	−0.03	−0.03	−0.23	0.19	0.18	0.00	−0.05	0.01
Age	0.27	0.01	0.08	0.12	−0.19	−0.16	−0.12	−0.17
Years of education	−0.11	−0.03	−0.36*	0.09	−0.07	−0.02	0.02	0.11
Handeness	0.02	0.16	0.05	0.37*	−0.12	−0.03	0.20	0.29
CAG repeats	0.10	0.31*	−0.03	0.10	0.25	0.46***	0.32*	0.11
Disease burden	0.33*	0.43***	0.08	0.22	0.15	0.41***	0.30*	−0.01
Clinical Performance								
TFC[a]	−0.32*	−0.55***	−0.42***	−0.31*	−0.08	−0.35*	−0.15	−0.24
UHDRS_TMS[b]	0.47***	0.61***	0.27	0.20	0.25	0.50***	0.10	0.07
MDRS[c]	−0.50***	−0.46***	−0.27	0.02	−0.24	−0.37*	−0.20	−0.15
Stroop	−0.46***	−0.53***	−0.29	−0.01	−0.21	−0.43***	−0.16	−0.01
Fluency	−0.24	−0.36*	−0.36*	0.06	−0.15	−0.37*	−0.13	−0.19
SDMT[d]	−0.46***	−0.60***	−0.20	−0.24	−0.31*	−0.40**	−0.22	−0.10

‘’ *(p > .05)* ; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$
[a] TFC = Total functional capacity
[b] UHDRS_TMS = Unified Huntington Disease Rating Scale motor score_Total Motor Score
[c] MDRS = Mattis Dementia Rating Scale
[d] SDMT = Symbol Digit Modality Test

other behavioral tasks and grey matter volume in gene carrier participants. To give more strength to this result, we confirmed the relationship between the striatum volume and performance in the temporal discrimination task (Estimate: −3.67; SE = 1.09; p < .001) when considering an independent striatum ROI, defined from an atlas (https://identifiers.org/neurovault.image:406338). Note that this analysis also included age, TIV and IRM type as a covariate. The ROI and the correlation are illustrated in Fig. 5C/D.

4. Discussion

The goal of the study was to investigate the specificity and the extent of the temporal deficit reported for patients with Huntington's Disease. To do so, we recruited three groups of participants (HD patients, Pre-HD and Controls) and measured their ability to process temporal information (durations in the seconds range) and spatial information (in the centimeters range) in three behavioral tasks (bisection, discrimination, and production). HD patients exhibited a clear deficit, yet more pronounced for time in the case of bisection and discrimination tasks. A questionnaire measuring disorientation in daily life confirmed the specific difficulties in the temporal domain of HD patients compared to controls. On the other hand, presymptomatic carriers of the mutated gene (Pre-HD) performed poorly the task of discrimination in the temporal but also spatial domains, presumably because of the high sensitivity of this task. Finally, using VBM analysis, we found a correlation between temporal discrimination performance and grey matter volume in the striatum in carriers of the mutated gene.

In comparison to previous studies, our behavioral findings confirm a deficit of HD patients in temporal information processing relative to age-matched (or older) healthy Controls, which has been consistently documented with various tasks (bisection: Beste et al., 2007; Paulsen et al., 2004; Righi et al., 2016 ; discrimination: Cope et al., 2014 ; production: Agostino et al., 2017; Beste et al., 2007; A. K. Rao et al., 2014). Our study allows us to determine whether the temporal processing deficit of HD patients is specific to time processing or reflect a more general impairment of HD patients in laboratory tasks. To do so, we tested patients not only in the temporal domain, but also in the spatial domain, in equivalent tasks in terms of complexity and cognitive demands. We found clear evidence supporting the idea that the deficit of HD patients is specific (or at least more pronounced) for the temporal domain. In both our bisection and discrimination paradigms, the deficit was present in both domains, but it was more pronounced in the temporal domain. In addition, with our questionnaire, HD patients reported more difficulties in daily life for time than for space, again in comparison to Controls. Altogether, our data point to a functional dissociation between spatial processing and temporal processing abilities, and a specific temporal deficit for HD patients. This deficit might be caused by a common factor underlying the different temporal tasks (indeed, performances were correlated across participants between temporal tasks, but less so between spatial tasks). These results are consistent with the possibility that an internal clock underlies different temporal processes, as postulated by the Striatal Beat Frequency Model (Meck, 2005; Teki,

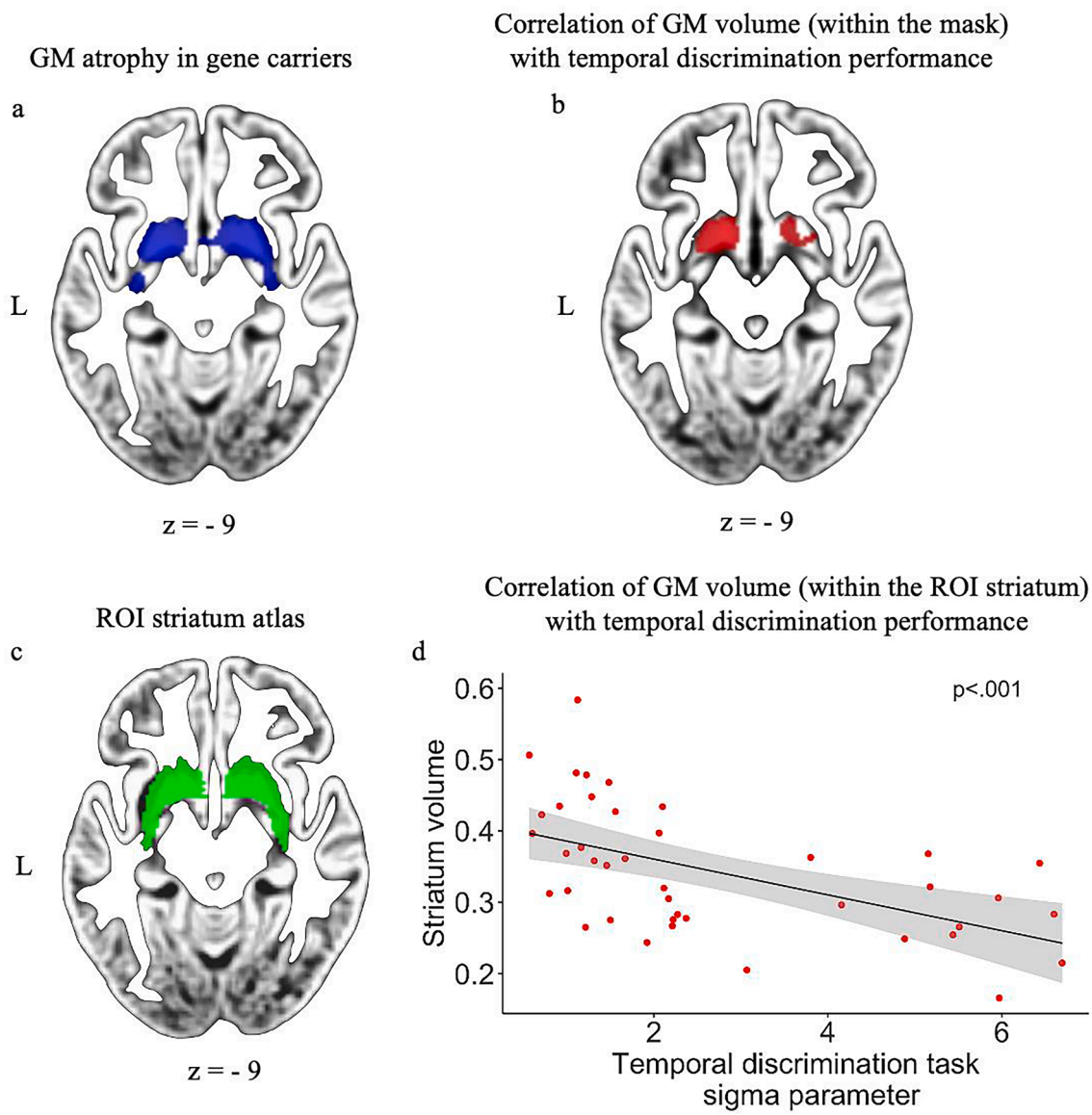

Fig. 5. Voxel-based morphometry in HD. (a) Regional grey matter atrophy in gene carrier participants relative to Controls (FWE-corrected, $p < .05$ for multiple comparisons with a threshold of at least 50 contiguous voxels) (b) For gene carrier participants, a correlation between grey matter volume and performance in the temporal discrimination task was found in the left putamen and right caudate (FWE-corrected, $p < .05$ for multiple comparisons with a threshold of at least 50 contiguous voxels). (c) Striatum ROI, defined by atlas: https://identifiers.org/neurovault.image:406338 (d) The striatum volume (as defined by the independent ROI) in gene carriers (y-axis) is reduced for participants exhibiting poorer performance in the temporal discrimination task (larger values of the σ parameter, x-axis) .

Grube & Griffiths, 2012).

The consistent results obtained for bisection and discrimination tasks, which both showed a greater impairment in the temporal domain for HD patients, is a striking aspect of our data. These tasks are quite different in procedure, and may be related to different aspects of temporal processing. Indeed, one may consider that our version of the discrimination paradigm involves some sort of rhythm detection. In our AAX procedure, the participant's task could be described as a judgment about the temporal regularity in the three onsets of the stimuli presented in the trial. This type of temporal information regarding a series of events is also referred to as relative timing (or beat-based timing) as opposed to absolute timing (or duration-based timing), which involves temporal intervals taken in isolation and not in a series (Grube et al., 2010a; Teki, Grube, Kumar & Griffiths, 2011; Teki, Grube & Griffiths, 2012), as in our temporal bisection and production tasks. Of note, relative timing is typically associated with the striatum, whereas absolute timing may be associated with cerebellum for sub-second durations and with the striatum for supra-second durations (Grahn & McAuley 2009; Grube et al., 2010b), which is the range we used in the present study.

In the discrimination paradigm, despite a more pronounced deficit for time, HD patients also showed a slight deficit in the spatial domain. We suggest that this reflects the high demands of the AAX task in terms of executive function. Indeed, the AAX task requires working memory, as it involves three stimuli, whereas both the bisection and production tasks involve a single stimulus. Discrimination also requires cognitive flexibility as the reference "A" randomly changed and needed to be updated from trial to trial. Finally, the discrimination task (15 min) was much longer than the other tasks (around 5 min), imposing more demands on sustained attention capacities. Given that working memory, attention and flexibility impairments are part of the cognitive deficits in HD (Ho et al., 2003; Lawrence et al., 1996), it would not be surprising if these functions participated in the observed impairment both in time and space discrimination in HD patients. The correlation found between the executive tasks (SDMT and Stroop) and discrimination tasks, both in time and space, supports this hypothesis.

In the production task, we acknowledge that the presence and the specificity of a deficit for HD patients remains unclear. Indeed, we found a difference between HD patients and Controls in the temporal task but not in the spatial task, however with no group × domain interaction. The lack of interaction could suggest a small deficit in HD patients in the spatial domain, which would be too small to be detected as such, but sufficient to undermine the group × domain interaction. One could be tempted to relate the suggested spatial deficit to the motor symptoms of HD, however our data does not confirm this relation, as we found no correlation between the spatial production task and the total motor score of UHDRS. Therefore, we suggest that future studies are needed to clarify this question.

Whereas our study shows a consistent pattern in HD patients, the results differ for Pre-HD participants, as in previous studies. PreHD allow getting rid of the motor deficits. They display a deficit relative to Controls only in the discrimination task, both in the temporal and spatial domain. Their temporal deficit in this task is consistent with the results of Paulsen et al. (2004), in a task where participants had to indicate which of two temporal intervals was longer. In contrast, the bisection task did not reveal any deficit, as in Beste et al. (2007) who also found no difference between Pre-HD participants and Controls in a task where participants had to indicate whether a stimulus corresponded to a long or a short reference previously learned. The production task yielded different results, with a deficit found in the studies by Rao et al. (2014) and Beste et al. (2007) but not here. One possible explanation for the discrepancy between our results and theirs might be the presence of feedback in the latter, which may have benefitted Control participants more than Pre-HD participants, given the involvement of the striatum in learning (Holl, Wilkinson, Tabrizi, Painold, & Jahanshahi, 2012).

The deficit of the mutant gene carriers with temporal tasks is consistent with their striatal atrophy and the role of the striatum for temporal processing. Previous fMRI studies have described striatal activation during temporal tasks both in Pre-HD participants (Paulsen et al., 2004; Zimbelman et al., 2007) and healthy participants (Coull, Nazarian & Vidal, 2008; Ferrandez et al., 2003; Pouthas et al., 2005; Rao, Mayer, & Harrington, 2001). Several studies have used VBM analyses and have linked striatal atrophy in HD to a number of cognitive deficits (e.g., Giavazzi et al., 2018; Hinzen et al., 2018; Tabrizi et al., 2013). Regarding the temporal deficit in gene carriers, grey matter volume in the caudate and putamen has also been related to response variability in a tapping task (Bechtel et al., 2010), which measures the temporal precision of the motor system. In the present study, we found that striatal grey matter volume was related to the precision of temporal discrimination, again supporting the role of the striatum in temporal processing. Note that this does not exclude the role of other neural (e.g. cortical) structures in temporal processing. Simply, as HD is primarily a degeneration of the striatum, the inter-individual variability in our sample was presumably more relevant to identify the role of the striatum than the role of any other structure. Contrary to what we expected, however, there was no additional association between the striatum and our other temporal tasks. We may speculate that the association between striatal volume and performance was greater for the temporal discrimination task compared to other temporal tasks, given the convergence of the temporal impairment with the high executive demands of the discrimination task (working memory, attention and flexibility). This relation with striatal grey matter volume was not found for spatial discrimination, in line with our behavioral results showing a greater deficit for time than for space in the discrimination task.

Finally, the deficit in temporal processing observed here in HD patients appears clinically relevant. Patients complain about difficulties in temporal organization in their daily life (e.g. they might be confused with respect to the time of the day) but they do not seem to lose themselves around their house, nor do they complain about space processing, as often acknowledged by their relatives and by medical staff. The disorientation questionnaire was designed to evaluate these difficulties. Indeed, our questionnaire indicated a specific temporal disorientation for HD patients, in the absence of spatial disorientation. Although we do not claim that this disorientation is a consequence of temporal deficits as measured in the behavioral tasks, we find that the correlation between temporal disorientation scores in the questionnaire and performances in the behavioral temporal tasks somewhat confirms the validity of the instrument. We also acknowledge that the present questionnaire may benefit from refinement. In particular, some questions are likely influenced by general factors such as executive skills, confidence or motivation, in addition to temporal or spatial disorientation. Nevertheless, this approach might already constitute a useful clinical instrument for HD patients. For Pre-HD participants, however, we note that no disorientation was evidenced with the questionnaire, and the only difference with Controls was found in the spatial and temporal discrimination tasks. Whether this questionnaire and temporal tasks could be used as preclinical markers of Huntington's disease deserves further investigation.

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Laurie Lemoine: Conceptualization, Methodology, Investigation, Resources, Software, Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Marine Lunven:** Formal analysis. **Blanche Bapst:** Investigation. **Laurent Cleret de Langavant:** Formal analysis. **Vincent de Gardelle:** Methodology, Formal analysis, Visualization, Writing – original draft, Writing – review & editing, Supervision. **Anne-Catherine Bachoud-Lévi:** Conceptualization, Methodology, Resources, Funding acquisition, Supervision, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102865.

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