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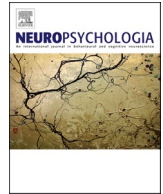
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The striatum in time production: The model of Huntington's disease in longitudinal study

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ABSTRACT

The unified model of time processing suggests that the striatum is a central structure involved in all tasks that require the processing of temporal durations. Patients with Huntington's disease exhibit striatal degeneration and a deficit in time perception in interval timing tasks (i.e. for duration ranging from hundreds of milliseconds to minutes), but whether this deficit extends to time production remains unclear. In this study, we investigated whether symptomatic patients (HD, N = 101) or presymptomatic gene carriers (Pre-HD, N = 31) of Huntington's disease had a deficit in time production for durations between 4 and 10 s compared to healthy controls and whether this deficit developed over a year for patients. We found a clear deficit in temporal production for HD patients, whereas Pre-HD performed similarly to Controls. For HD patients and Pre-HD participants, task performance was correlated with grey matter volume in the amygdala and caudate, bilaterally. These results confirm that the striatum is involved in interval timing not only in perception but also in production, in accordance with the unified model of time processing. Furthermore, exploratory factor analyses on our data indicated that temporal production was associated with clinical assessments of psychomotor and executive functions. Finally, when retested twelve months later, the deficit of HD patients remained stable, although striatal degeneration was more pronounced. Thus, the simple, short and language-independent temporal production task may be a useful clinical tool to detect striatal degeneration in patients in early stages of Huntington's disease. However, its usefulness to detect presymptomatic stages or for monitoring the evolution of HD over a year seems limited.

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1. Introduction

Huntington's disease (HD) is a genetic neurodegenerative disease, defined as the autosomal dominant transmission of an expansion of the trinucleotide CAG-repeats within the huntingtin (Htt) gene on the short arm of chromosome 4. The diagnosis is made at the emergence of motor symptoms (chorea, dystonia, and gait disturbances), which typically occur in mid-life. This disease causes prominent cell loss with atrophy in the caudate and putamen, affecting the medium spiny neurons in the striatum (Graveland et al., 1985; McColgan et al., 2017; Vonsattel and DiFiglia, 1998). The striatum is also affected in the premanifest stage of HD (Pre-HD) (Tabrizi et al., 2013), which corresponds to individuals carrying the huntingtin mutation but not yet exhibiting the motor symptoms associated with HD.

Although the clinical diagnosis is only based on motor symptoms, HD patients also display a range of psychiatric disorders (mostly depression and anxiety) and cognitive deficits (affecting executive functions in particular) detrimental for them and their families. Among those, HD patients often report difficulties with temporal processing in their daily life. These difficulties are very disabling, as we know that time is crucial for various cognitive processes, such as decision-making (Gallistel, 1990; Richelle & Lejeune, 1980), rate estimation (Brighouse et al., 2014; Gibbon & Gallistel, 2000), multiple-step arithmetic (Sohn & Carlson, 2003), learning and memory (Gallistel & Balsam, 2014).

In the present study, we investigate the processing of temporal information in patients with Huntington's disease. Indeed, patients and their caregivers report temporal processing difficulties related to HD, hampering the daily life. These difficulties are consistent with the degeneration of the striatum in HD and with the key role of the striatum in temporal processing. Indeed, a large body of research in humans (including healthy volunteers and patients) and rats (see e. g. Buhusi and Meck, 2005 for a review) shows that the striatum has a central role in interval timing tasks (i.e. tasks focusing on temporal durations from hundreds of milliseconds to minutes). In particular, according to the prominent Striatal Beat Frequency model (Meck et al., 2008; Oprisan and Buhusi, 2011), medium spiny neurons in the dorsal striatum hold the role of an internal clock that underlies temporal judgments (Ivry and Schlerf, 2008; Treisman, 1963). One further question is whether the temporal deficit in HD patients concerns both perception and production of temporal durations. Indeed, according to the unified model of time (Teki et al., 2012), the striatum would be involved in all types of temporal tasks. However, although the deficit of HD patients is well established in perception tasks (Beste et al., 2007; Cope et al., 2014; Lemoine et al., 2021; Righi et al., 2016), their ability in tasks involving the production of temporal durations is unclear.

Two studies have reported a deficit in a reproduction task in HD patients (Agostino et al., 2017; Rao et al., 2014) and in Pre-HD participants (Agostino et al., 2017; Rao et al., 2014). However, reproduction involves both perception and production as participants are first

presented with a duration (in the range of seconds), and have to reproduce that duration. Two other studies have used a paradigm where participants had to produce a specific duration (1200 ms) that was not presented to them, but was learnt over trials from the feedback received after each attempt (Beste et al., 2007; Wild-Wall et al., 2008). Rather than difficulties with temporal production per se, the deficit reported in these two studies could thus reflect difficulties with learning from feedback, which have also been documented in HD patients (Palminteri et al., 2012). Finally, one recent study reported no clear deficit in temporal production, in a task where participants had to produce (without feedback) a temporal duration from 4 to 10 s, however the number of patients may have been insufficient in this study (Lemoine et al., 2021). Thus, more evidence is needed to establish unambiguously the deficit in temporal production for HD patients and for Pre-HD participants. Demonstrating this deficit is important to support the unified model of time (Teki et al., 2012), acknowledging the mandatory role of the striatum for all timing tasks.

To address this issue, in the present study we assessed temporal production tasks in a large cohort of HD patients (N = 101), Pre-HD participants (N = 31) and healthy participants (Controls, N = 69). We also conducted voxel-based morphometry (VBM) analyses to assess whether behavioral performances would correlate with striatal atrophy in patients, to further evaluate the role of the striatum in temporal production. We also conducted exploratory factor analyses to identify the clinical components that could be involved in the temporal production task. Besides, Control participants and HD patients were tested three times (once at baseline, then again one month after baseline, and one year after baseline), in order to evaluate whether temporal production might be a good tool for future therapeutic trials.

2. Materials and methods

2.1. Participants

One hundred and thirty two carriers of the Huntingtin (Htt) gene (CAG repeats ≥ 38), including 31 Pre-HD (Total Functional Capacity scores = 13 and Total Motor Scores of Unified Huntington Disease Rating Scale ≤ 5) and 101 HD patients at an early stage of the disease (stage I and II, according to their Total Functional Capacity scores; Shoulson, 1981) were enrolled in the study, together with 69 healthy participants (Controls). Data of 20 Pre-HD participants were already included in Lemoine et al. (2021). The burden score, an index of disease burden, was calculated from the formula (age x [CAG-35.5]) (Penney et al., 1997). In addition, 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 6.8 years from onset). All groups were matched for

Table 1

Demographic data for Pre-HD participants, HD patients and Controls. Participants in the Pre-HD group were further divided into Close from onset and Far from onset based on estimated onset. See Table 2 for clinical scores at M0.

	Pre-HD	Pre-HD Close	Pre-HD Far	HD	Controls
Number of participants	31	15	16	101	69
Sex	11 M/20 W	6 M/9 W	5 M/11 W	66 M/35 W	34 M/35 W
Age (years)	43.9 \pm 1.6	46.7 \pm 2	41.3 \pm 2.5	52.7 \pm 1.1	51.2 \pm 1.3
Education (years)	13.8 \pm 0.5	14 \pm 0.7	13.7 \pm 0.3	14 \pm 0.3	14 \pm 0.4
Handedness	28 R/3 L	14 R/1 L	14 R/2 L	3 A/94 R/4 L	2 A/61 R/6 L
Disease duration (years)	-	-	-	4 \pm 0.4	-
Number of CAG repeats	42.8 \pm 0.5	44 \pm 0.7	41.8 \pm 0.6	43.5 \pm 0.3	-
Estimated onset	6.7 \pm 1.6	-0.4 \pm 1.3	13.3 \pm 1.6	-	-
Disease burden score	309 \pm 16.4	377.4 \pm 19.5	244.8 \pm 11.7	394.1 \pm 9.4	-

W = women, M = men, R = right-handed, L = left-handed, A = ambidextrous. Estimated onset: number of years before the estimated onset.

years of education ($F(2,196) = 0.03; p = .97$) and handedness ($\chi^2 = 3.02, df = 4, p = .55$) (see Table 1 for the demographic data). Pre-HD participants and controls were matched for sex ($\chi^2 = 1.14, df = 1, p = .287$) but there were more men in the HD patients than in controls ($\chi^2 = 10.06, df = 2, p = .006$) and in Pre-HD ($\chi^2 = 7.52, df = 1, p = .006$). HD patients and controls were matched for age ($t(150.71) = 0.93, p = .4$) Pre-HD participants were younger than controls ($t(67.85) = -3.45, p < .001$) and HD ($t(61.04) = -4.43, p < .001$). HD patients and controls were recruited from 4 sites (Cardiff, UK; Créteil, France; Manchester, UK; and Muenster, Germany) participating in a European observational longitudinal study (Repair-HD, <http://www.repair-hd.eu>), which aims to establish a new protocol for assessing innovative therapies in Huntington's disease. This study, called the CAPIT-HD Beta study (NCT 03119246) obtained ethics approval from a French research ethics committee (CPP Ile de France III). Pre-HD participants 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

All participants were evaluated with the Unified Huntington's Disease Rating Scale (UHDRS, Kieburts et al., 2001) which includes the Total functional capacity (TFC), the Total Motor Score (TMS), the Letter Verbal Fluency Task over 1 min, the Symbol Digit Modalities Test (SDMT), and the Stroop tests (Color, Word and Interference). In addition, participants performed the Mattis Dementia Rating Scale (MDRS; Mattis, 1976), the Animal verbal fluency task over 1 min (Cardebat et al., 1990) and the Hopkins Verbal Learning Memory Test (HVLMT; Brandt, 1991).

2.3. Temporal production task

The temporal production task was taken from our previous study (Lemoine et al., 2021). On each trial, participants were presented with an integer between 4 and 10, indicating the duration in seconds that they would have to produce in that trial. They then had to press the spacebar on the keyboard, which made a black dot appear on the screen, and to press it again when they considered that this dot had been on the screen for the requested duration. Each duration was presented three times in a random order, resulting in 21 trials. No feedback was provided to participants. A training phase of two trials preceded the test phase to ensure that the task was understood. The task lasted 5 min on average. Stimulus presentation and response recording were performed in Python, using the Psychopy toolbox (<https://www.psychopy.org/>), and the task was completed on different laptops in the different centers.

As in Lemoine et al. (2021), we analyzed participants' performance in the temporal production task by examining how the produced duration y could be predicted from the requested duration x , in a linear regression ($y = ax + b$). We fitted this linear regression for each participant, and evaluated performance using the standard deviation of the residual error in this regression, hereafter σ , which quantifies the noise in the production responses (see Fig. 1 for an example). The value of σ corresponds to the variation of a participant's productions for a given stimulus level. Lower values of σ correspond to better performance, with participant responses being less variable for a given requested duration. We also computed the bias in temporal production responses, that is, the mean response minus the mean requested duration (i.e. 7 s), for each participant. This bias allows us to identify whether participants are underestimating or overestimating elapsed time.

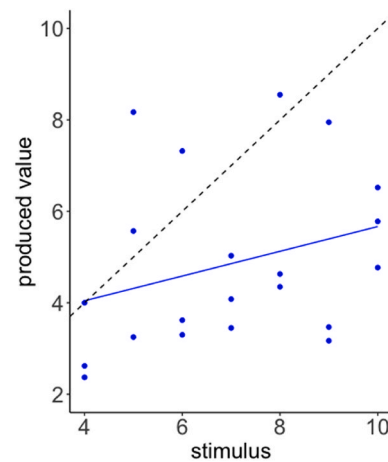


Fig. 1. Example of behavioral performance for a single HD patient. The dots correspond to individual trials, and the parameter of interest σ corresponds to the jitter (along the y-axis) of the dots relative to the best-fit line.

2.4. MRI scanning and preprocessing

Brain MRI was optional and acquired in two centers in our study, either at Henri Mondor Hospital (Créteil, France), on a Siemens Skyra including T1 3D anatomical MP-RAGE images (repetition time: 2300 ms; echo time: 2900 ms; inversion time: 900 ms; flip angle: 9; acquisition matrix: 256×240 ; slice thickness: 1.2 mm, no inter-slice gap, 176 sagittal sections), or at the George Huntington Institute (Muenster, Germany), on a Philips Medical Systems including T1 3D anatomical MP-RAGE images (repetition time: 6770 ms; echo time: 3130 ms; inversion time: 900 ms; flip angle: 9; acquisition matrix: 256×256 ; slice thickness: 1.2 mm, inter-slice gap: 1.2 mm, 170 sagittal sections).

As a result, 138 participants (60 HD patients, 25 Pre-HD participants and 53 Controls) underwent structural brain MRI at baseline. With these participants, all groups were matched for years of education ($F(2,134) = 0.72; p = .49$) and handedness ($\chi^2 = 3.43, df = 4, p = .49$). Pre-HD participants and controls were matched for sex ($\chi^2 = 1.14, df = 1, p = .71$). There were more men in the HD patients than in controls ($\chi^2 = 6.15, df = 1, p = .01$) and in pre-HD ($\chi^2 = 10.52, df = 2, p = .005$). HD patients and controls were matched for age ($t(110.95) = 0.58, p = .56$). Pre-HD participants were younger than controls ($t(56.28) = -3.32, p = .002$) and HD ($t(62.45) = -3.74, p < .001$). Among these participants, 30 HD patients and 30 Controls also underwent brain MRI at M12.

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 (<https://www.mathworks.com/>). Structural images were corrected for intensity bias, classified by tissue and registered, by linear and non-linear transformations (DARTEL) within a unified model (Ashburner and 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. We used a dedicated segmentation implemented in SPM for longitudinal data, as a voxel or point wise comparability need to be assured not only across subjects, but also across time points within subjects. Subsequently, the resulting images are processed in the same way as cross-sectional data.

2.5. Procedure

All participants (69 Controls, 101 HD patients, and 31 Pre-HD participants) who were included performed motor, functional, cognitive assessments and temporal production task at baseline (M0). Longitudinal follow-up was proposed optionally only to HD patients and to Controls, and adapted to the staff of each centre. One month later (M1), 157 of these participants (64 Controls and 93 HD patients) completed the same cognitive evaluations and the temporal production task again. This additional baseline allows to limit the retest effect (Schramm et al., 2015). Pre-HD participants were not included in the follow-up study, and some HD patients and Controls did not complete the M1 follow-up session due to a shortage of specialists for this assessment in some centers. Finally, 114 of these participants (48 Controls and 66 HD patients) performed motor, functional, cognitive assessments, and the temporal production task 12 months after baseline (M12).

2.6. Statistical analyses

2.6.1. Temporal production task and clinical scores

Statistical tests were performed in R (<https://www.r-project.org/>). Missing data in the cognitive tests used in the clinical assessment (see Table 2, except for TFC and TMS which are not cognitive tests) were imputed using the “missForest” package. We performed analyses of variance (ANOVAs) with group (Controls, Pre-HD, and HD), session (M0, M1, and M12) and their interaction as independent factors, and including age and sex as covariates. We ran additional Student’s *t*-test to evaluate pairwise comparisons of groups. Effect sizes calculated as omega-squared (ω^2) (for small sample sizes, ω^2 reduces bias; Lakens, 2013) and reported only for $F > 1$. We considered ω^2 of 0.01, 0.06, 0.14 as small, medium and large effect sizes, respectively (Kirk, 1996). We evaluated the correlation between performances for the temporal production task, the results of clinical assessment tests, and demographic data, with Pearson’s correlation. Finally, exploratory factor analysis, using oblimin rotation, was conducted using the ‘fa’ function from the R package psych (Revelle, 2021) and the “EFA” function from the R package EFAtools (Steiner et al., 2021). Scree plot was produced using the *parallel* function in R, and we considered the standard fit indices: Root Mean Square Error of Approximation (RMSEA), Comparative Fit Index (CFI), Bayesian Information Criteria (BIC).

2.6.2. MRI data analysis

VBM analyses investigated regional differences between gene carrier participants (HD and Pre-HD) and Controls at baseline, in terms of smoothed, modulated and normalized grey matter volume and delineated grey matter atrophy. Our approach was similar to previous studies looking at correlations between VBM and cognitive performance in HD patient (Giavazzi et al., 2018; Lemoine et al., 2021). 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, sex, total intracranial volume (TIV), and the type of MRI sequence used as covariates. An atrophy mask was created for subsequent analyses, which included the clusters showing a significant effect of group in this analysis (FWE-corrected, $p < .05$ with at least 50 contiguous voxels). Significant clusters were anatomically labeled by superimposing the statistical parametric maps on the AAL atlas implemented in MRICron software (<http://www.mricron.org>).

Using the data at baseline (M0), we then investigated the relation between grey matter volume and performance in the temporal production task in the gene carrier participants ($N = 85$) within this atrophy mask. To do so, we conducted a linear regression across participants where age, sex, TIV and MRI type were included as covariates. Again, statistical outcomes were based on FWE-corrected $p < .05$ and a minimum of 50 voxels per cluster. For each gene carrier participant, we used FSL (<https://fsl.fmrib.ox.ac.uk/>) to extract the mean probability of GM values within the significant clusters, for illustration purposes.

For longitudinal analyses, we used a flexible factorial model in SPM to test the interaction between groups (HD patients and Controls) and sessions (M1 and M12) on tissue volume, within the atrophy mask (again using FWE-corrected $p < .05$ with at least 50 voxels per cluster, and including age, sex, TIV and MRI type as covariates). We then used FSL to extract longitudinal differences in grey matter volume (M12 minus M1) for each participant, and regressed these values against longitudinal differences in temporal production performances (sigma at M12 minus sigma at M1), in the 30 HD patients

3. Results

3.1. Temporal production task at baseline

First, behavioral performance showed a deficit of HD patients in the temporal production task (Fig. 2). Specifically, an ANOVA on the parameter σ , which quantifies the variability of responses to a given duration, indicated a main effect of group ($F(2,196) = 12.12, p < .001, \omega^2 = 0.15$). There was also a main effect of age ($F(1,196) = 5.79, p = .02, \omega^2 = 0.05$) but no effect of sex in this analysis. To better characterize the group effect on σ we compared HD patients to Controls, and Pre-HD participants to Controls, in separate ANOVAs. We found that HD patients were impaired relative to Controls ($F(1,166) = 18.15, p < .001, \omega^2 = 0.15$) but Pre-HD participants were not ($p > .97$). In sum, HD patients but not Pre-HD participants exhibited a deficit in temporal production. In addition, we performed additional analyses with a subsampling strategy to validate the main results while controlling for differences in sample sizes between groups. Specifically, when comparing two groups, we randomly selected participants from the larger group to obtain a sample size equal to that of the smaller group, and we conducted the

Table 2
Clinical scores at baseline (M0).

	Pre-HD	HD	Controls	p values	
				Pre-HD vs Controls	HD vs Controls
TFC	13 ± 0	10.5 ± 0.2	13 ± 0	1	<.001
TMS	0.61 ± 0.2	29.8 ± 1.45	0.81 ± 0.16	0.47	<.001
Letter Fluency	39.3 ± 1.99	27.9 ± 0.92	41.99 ± 1.2	0.26	<.001
Animal Fluency	18.7 ± 0.83	14.1 ± 0.47	22.1 ± 0.72	.003	<.001
SDMT	50.3 ± 2.14	30.5 ± 0.98	51.2 ± 1.3	0.72	<.001
Stroop Color	74.6 ± 2.45	48.9 ± 1.39	78.6 ± 1.38	0.17	<.001
Stroop Word	98.1 ± 2.82	68.5 ± 1.70	101.2 ± 1.77	0.36	<.001
Stroop Interference	46.3 ± 1.94	27.7 ± 0.87	46.07 ± 1.16	0.93	<.001
MDRS	140.1 ± 0.92	132.1 ± 0.8	141.6 ± 0.28	0.12	<.001
HVLT - IR	24.9 ± 1.11	19.1 ± 0.59	27.4 ± 0.49	0.04	<.001
HVLT - DR	9.09 ± 0.49	5.72 ± 0.3	9.9 ± 0.26	0.15	<.001

TFC Total Functional Capacity, TMS Total Motor Score, SDMT Symbol Digit Modalities Test, MDRS Mattis Dementia Rating Scale, HVLT Hopkins Verbal Learning Test, IR Immediate Recall, DR Delayed Recall. P-values correspond to t-tests (uncorrected for multiple comparisons).

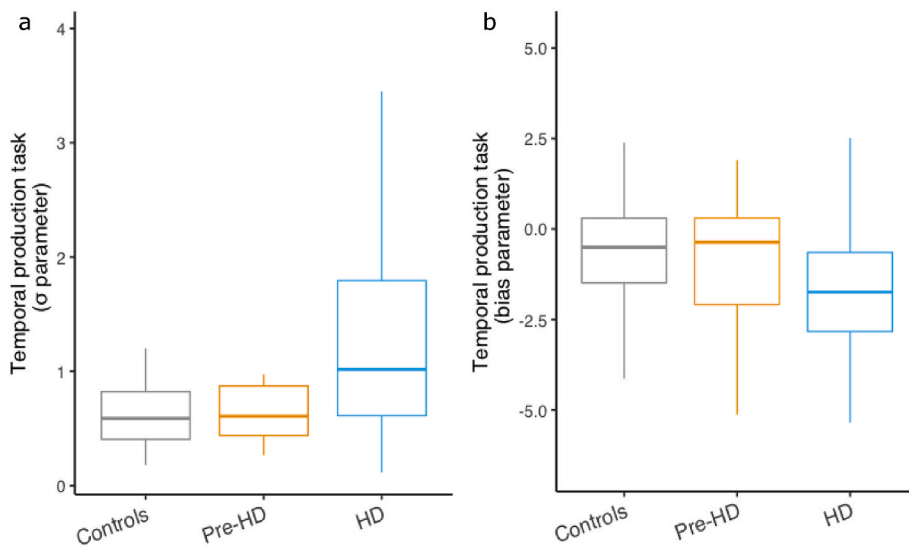


Fig. 2. Temporal production performance. (a) For each group, boxes and hinges represent the median of the σ parameter the temporal production task, together with the first quartile (Q1), and third quartile (Q3). The two lines extend each boxplot to 1.5 times the interquartile range above and below these quartiles. Lower values of σ correspond to better performances. (b) Performance measures (bias parameter) in the temporal production task for each group. Negative (resp. positive) bias values correspond to underestimations (resp. overestimations) of temporal durations.

ANOVA on this data. The procedure was then repeated 5000 times (with different subsamples of the larger group) to obtain a distribution of the test statistic. In brief, these analyses confirmed the results that HD patients performed worse than Pre-HD and Controls participants (see Supplementary Material for details).

We also examined the bias in the temporal production task, defined as the mean duration produced by participants minus the mean

requested duration, for the different groups. We observed a significant negative bias, indicating that all groups produce temporal durations that are too short on average ($t(100) = -7.08, p < .001$), Pre-HD ($t(30) = -2.35, p = .03$) and Controls ($t(68) = -2.95, p = .004$). Groups differed regarding the size bias ($F(2,196) = 4.43, p = .01, \omega^2 = 0.07$). Separate ANOVAs further indicated that the bias was more pronounced in HD patients compared from Controls ($F(1,166) = 8.31, p < .001, \omega^2 = 0.06$)

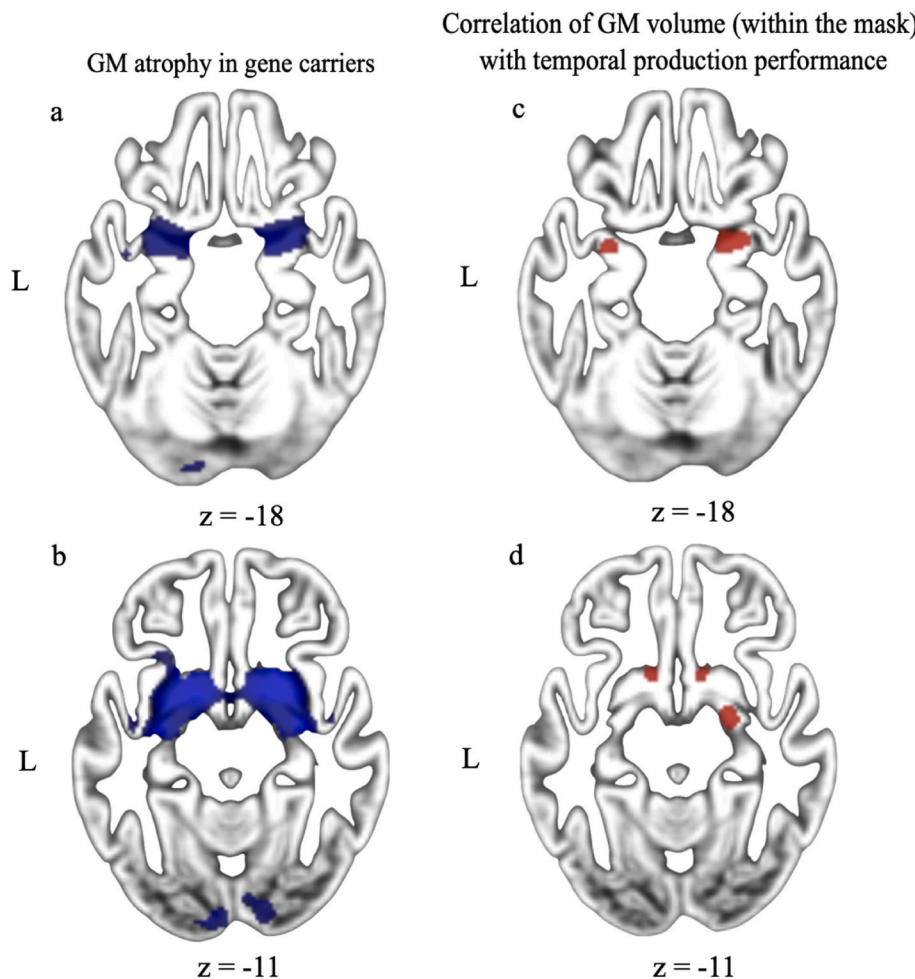


Fig. 3. Voxel-based morphometry in gene carriers. (a) Regional grey matter atrophy in gene carrier participants relative to Controls in $z = -18$, and (b) in $z = -11$ (FWE-corrected, $p < .05$ for multiple comparisons with a threshold of at least 50 contiguous voxels). (c) For gene carrier participants, a correlation between grey matter volume and the σ parameter in the temporal production task was found in the right and left amygdala, and (d) in the left and right caudate (FWE-corrected, $p < .05$ for multiple comparisons with at least 50 contiguous voxels).

and Pre-HD participants, who behave similarly ($p > .7$).

In order to detect potential behavioral signs of HD before the onset of motor symptoms, following previous studies, we also examined if Pre-HD Close) or far Pre-HD Far discriminated. Controls, Pre-HD Far and Pre-HD Close participants behave similarly in pairwise tests, both for the σ parameter (all $p > .29$) and for the bias parameter (all $p > .32$).

3.2. Voxel-based morphometry

To confirm that temporal production performances were associated with the striatum, we conducted VBM analyses on MRI data in our participants at baseline. As expected, grey matter volume in gene carrier participants (Pre-HD and HD patients) was smaller than in Controls, especially in the striatum (both left and right putamen, see Fig. 3A) but also in the amygdala (Fig. 3B) (see Supplementary Table A for details). Within the mask comparing patients and controls, we examined the correlation between the σ parameter in the temporal production task and grey matter volume in gene carriers, while including age, sex, TIV and MRI type as covariates. Four clusters exhibited a negative correlation ($p < .05$, FWE-corrected with at least 50 voxels): two in the amygdala (right: MNI coordinates $x,y,z = 28,-4,-15$; $T = 5.13$; cluster size = 544 voxels; left: $x,y,z = -30,-3,20$; $T = 4.72$; cluster size = 66 voxels; see Fig. 3C), and another two in the caudate (left: $x,y,z = -15,8,-14$; $T = 4.41$; cluster size = 73 voxels; right $x,y,z = 10,6,-15$; $T = 4.39$; cluster size = 51 voxels; see Fig. 3D). The relationship between individual values of temporal performance and of grey matter volume in these clusters are illustrated in Supplementary Figure B. We also conducted the same analysis on bias instead of σ but no significant clusters were found in this case.

3.3. Correlation with clinical scores and factor analyses

In order to investigate the nature of the temporal production deficit in HD patients, our next analysis consisted in examining the relation between temporal production performances and scores in a set of clinical tests, at baseline. Note that HD patients performed worse than Controls for all clinical scores at baseline (Table 2), whereas Pre-HD participants performed worse than Controls only in one task (the Animal fluency task). Besides, Pre-HD Close and Pre-HD Far participants

Table 3

Exploratory factor analysis on clinical performance. Upper panel: Loadings for the different clinical tests are reported for each factor. Lower panel: regression coefficient and p-value, in a multivariate regression across HD patients and Pre-HD participants, where the σ parameter in the temporal production task was predicted from the scores for each factor.

Component	Factor 1	Factor 2	Factor 3
TFC	.593	.130	.089
TMS	-.664	-.019	-.236
Letter Fluency	.111	.689	.047
Animal Fluency	.321	.610	-.039
SDMT	.607	.253	.262
Stroop Word	.715	.248	.020
Stroop Effect	.606	-.089	-.071
MDRS_Attention	-.063	.408	.084
MDRS_Initiation	.200	.610	.019
MDRS_Construction	-.025	.160	.127
MDRS_Concept	-.030	.598	-.073
MDRS_Memory	.028	.434	.239
HVLM-IR	.042	-.035	.932
HVLM-DR	.094	.076	.802
Relation with σ in	Estimate =	Estimate =	Estimate =
Temporal production	-0.26 $p = .002$	-0.05 $p = .46$	-0.16 $p = .07$

TFC Total Functional Capacity, TMS Total Motor Score, SDMT Symbol Digit Modalities Test, MDRS Mattis Dementia Rating Scale, Stroop Effect = Stroop Color – Stroop Interference, HVLM Hopkins Verbal Learning Test, IR Immediate Recall, DR Delayed Recall.

performed similarly on all clinical tests (all $p > .16$).

We found that the σ parameter correlated with most clinical scores (the full correlation matrix is reported in Supplementary Table B). This indicates that the results of this simple and short behavioral task is consistent with the typical tools used for clinical diagnosis. We did not find correlation between σ and the estimated disease onset in the Pre-HD group ($r = 0.26$, $p = .16$), consistent with the absence of difference between Pre-HD far and close participants on this measure. There were no correlations between the bias parameter and the clinical scores (all $p > .45$).

An exploratory factor analysis investigated the factorial structure of clinical scores in gene carrier participants. Our N/p ratio (132/14 = 9.43) indicated that we had enough power for a factor analysis, our Kaiser-Meyer-Olkin measure of sampling adequacy of 0.87 was above the recommended value of 0.50, and Bartlett's test of sphericity was significant ($\chi^2(91) = 985.86$, $p < .001$), indicating that the data were suitable for factor analysis (Hair et al., 2006). Examination of the scree plot and fit indices suggested that a 3-factor structure was the most appropriate reduction of the data ($\chi^2(52) = 110.52$, $p < .001$, RMSEA = 0.09 (90% CI = 0.07–0.12), CFI = 0.97, BIC = -151.88). In particular, BIC was smaller (indicating a better fit) for the three-factor model compared to solutions with 2 factors (BIC = -143.38) or 4 factors (BIC = -126.35).

Table 3 illustrated the loadings associated with the 3 factors solution. In particular, the three factors can be associated respectively with psychomotor/executive skills, language production, and memory. Indeed, the first factor shows high loadings for the Total Functional Capacity, Total Motor Score, Symbol Digit Modalities Test, Stroop Word, Stroop Effect (Stroop Color - Stroop Interference) and Animal Fluency. Fluency scores and the different sub-components of Mattis Dementia Rating Scale, except Construction, loaded highly onto the second factor. Finally, memory scores (immediate recall and delayed recall in the Hopkins Verbal Learning Test) loaded highly onto the third factor. Importantly, a multivariate regression across participants indicated that values of σ in the temporal production task were associated with individual values on the first factor ($p = .002$), but not with the others (all $p > .07$). Individual values of bias in the temporal production task were not related to any of the 3 factors (all $p > .08$). In other words, poor performance (high response variability) in temporal production was associated in clinical evaluations with psychomotor/executive deficits, rather than with language or memory deficits.

3.4. Longitudinal analyses from M0 to M12

Behavioral performance in the temporal production task appeared stable across the three sessions. The group x session ANOVA on both the parameter σ and the bias indicated a main effect of group, but no main effect of session and no group x session interaction (see Table 4). In other words, temporal production performance of HD patients did not decline over a year.

By contrast, VBM analyses revealed a small but significant neural degeneration in HD patients as expected (Tabrizi et al., 2013). Specifically, when comparing 30 HD patients to 30 Controls for whom we could obtain MRI data both at M1 and M12, we found an interaction between groups (HD patients and Controls) and sessions (M1 and M12), with a progressive reduction in right caudate volume observed in HD patients between M1 and M12 but not in Controls ($x,y,z = 9,14,2$; $T = 6$, 54 , $p < .05$, FWE-corrected; cluster size = 59 voxels). This indicates that VBM analyses were sensitive enough to detect the evolution of the disease in HD patients relative to controls, even on a small subsample of participants. For completeness, we examined whether longitudinal differences (M1 minus M12) in grey matter volume would correlate in gene carriers with longitudinal differences in performance (as assessed by σ or bias) in the temporal production task, but we found no significant cluster of correlation.

Clinical scores declined in HD patients over a year. Significant group

Table 4

(Left) ANOVAs for temporal production task and clinical tests, with main effects of session (M1 vs. M12) and group (HD patients vs. Controls) and their interaction. (right) For temporal production task and clinical tests, we evaluated session effects separately in HD patients and Controls, as the difference in the score obtained in the M1 session minus the M12 session (see Table D in supplementary material for clinical scores at M12 session). Note that except for σ and bias parameter, TMS and Stroop Effect, clinical scores are coded with higher values for better abilities, such that positive values of session effects indicate a decline in the ability over a year.

	Group effect	ANOVA		T-tests				
		Session effect	Group*Session interaction	HD		Session effects (M1-M12)		
				M \pm SD	p-values	M \pm SD	Controls	p-values
Temporal Production								
σ parameter	.001	.71	.26	-0.01 \pm 0.14	.95	0.03 \pm 0.06		.59
Bias parameter	.001	.95	.12	-0.34 \pm 0.20	.09	0.14 \pm 0.21		.50
Clinical scores								
TFC	.001	.001	.001	0.83 \pm 0.19	.001	0 \pm 0		
TMS	.001	.02	.02	-2.43 \pm 1.14	.04	0.16 \pm 0.12		.17
Letter Fluency	.001	.009	.002	2.32 \pm 0.95	.02	0.56 \pm 0.98		.57
Animal Fluency	.001	.13	.03	1.30 \pm 0.50	.01	-0.18 \pm 0.80		.82
SDMT	.001	.01	.001	2.19 \pm 0.56	.001	0.12 \pm 0.77		.87
Stroop Word	.001	.34	.001	4.37 \pm 1.42	.003	-2.78 \pm 1.58		.09
Stroop Effect	.001	.19	.68	-0.13 \pm 1.05	.9	-0.30 \pm 1.27		.81
MDRS	.001	.009	.05	2.41 \pm 0.76	.002	0.14 \pm 0.32		.66
HVLMT-IR	.001	.11	.09	0.89 \pm 0.53	.09	0.02 \pm 0.42		.96
HVLMT-DR	.001	.03	.02	0.70 \pm 0.30	.02	-0.14 \pm 0.22		.51

TFC Total Functional Capacity, TMS Total Motor Score, SDMT Symbol Digit Modalities Test, MDRS Mattis Dementia Rating Scale, Stroop Effect = Stroop Color – Stroop Interference, HVLMT Hopkins Verbal Learning Test, IR Immediate Recall, DR Delayed Recall.

\times session interactions were found for most clinical scores, with significant deterioration in HD patients but not in Controls (see Table 4). To go further, we examined whether the different clinical scores evolved in a similar way across sessions, by looking at the correlations in these declines (see Supplementary Table C). Only two correlations survived statistical correction: one between the Symbol Digit Modalities Test and the Total Motor Score, and another one between the two components of the Hopkins Verbal Learning Memory Test (immediate recall and delayed recall). Given the lack of correlations in these declines, exploratory factor analysis could not be considered. Nonetheless, we note that for temporal production (σ parameter), the largest correlations were found with TMS and SDMT scores, which is consistent with the results of the factor analysis at baseline. For bias, no correlations were found between the evolution of bias over a year and the evolution of clinical scores.

4. Discussion

The goal of the study was to investigate temporal production performance in patients with Huntington's disease. To do so, we recruited HD patients, Pre-HD and Controls, and we followed HD patients and Controls longitudinally one month and twelve months after the baseline session. At baseline, HD patients exhibited a clear deficit in temporal production task, with more variable responses and a greater underestimation of temporal durations, compared to Controls. By contrast, pre-symptomatic carriers of the mutated gene (Pre-HD) performed similar to Controls. Temporal production variability was correlated with grey matter volume in the caudate, confirming the role of the striatum in temporal production. Overall, these results are in line with the unified model of temporal processing, which proposes a central role of the striatum in both perception and production tasks, and thus predicts a deficit in temporal production for HD patients. Further analyses in our data pointed at a relation between variability of temporal productions and psychomotor and executive functions, as assessed by standard clinical tests. Finally, the longitudinal follow-up of HD patients and Controls did not show a decline across sessions of temporal production performances, although VBM analyses and clinical evaluations could detect a degradation of HD patients relative to Controls.

Our behavioral findings establish a clear deficit of HD patients in a pure temporal production task, which unlike previous studies, does not involve additional components such as temporal perception (Agostino et al., 2017; Rao et al., 2014) or learning capacities (Beste et al., 2007;

Wild-Wall et al., 2008). Behaviorally, this deficit was observed on two measures: patients exhibited a high variability of responses when requested to produce a specific duration, and they underestimated temporal duration when producing time (as was also found in Agostino et al. (2017), and at least qualitatively in Wild-wall et al. (2008)). Response variability was correlated with both striatal degeneration and clinical scores which is a general hallmark of HD (Bachoud-Lévi et al., 2001). A possible account for the underestimation of temporal duration in HD is the deficit of attention in these patients (e.g., as documented by the SDMT in our study). Indeed, previous research has shown that temporal durations are judged as shorter when fewer attentional resources are engaged towards temporal information (Zakay, 1989). One could also speculate that this underestimation of time might be related to the impulsivity of HD patients, which has been documented with questionnaires (Johnson et al., 2017) or with inhibitory control tasks (Júlio et al., 2019), but we acknowledge that further research is needed to examine this issue more specifically.

Together with previous studies, our result establishes that the deficit in temporal processing in HD patients thus includes not only perception (Beste et al., 2007; Cope et al., 2014; Lemoine et al., 2021; Righi et al., 2016) but also production. The striatal atrophy in gene carriers measured by VBM is linked to lower performance in tapping task (Bechtel et al., 2010), temporal discrimination task (Lemoine et al., 2021), and, here, time production as well. These results provide a convergent picture of the role of the striatum in temporal processing (e.g. Buhusi and Meck, 2005), irrespectively of the particular task at hand. This supports the unified model of time (Meck, 2005; Teki et al., 2012) which assigns a key role to the striatum. In this model, distributed cortical circuits contain a population of neurons oscillating at different frequencies, and the medium spiny neurons in the dorsal striatum act as coincidence detectors capturing the beats of the cortical oscillators.

Here, VBM analyses showed a correlation between amygdala volume and precision of temporal production in gene carriers. To our knowledge, previous studies using VBM have never highlighted this region in relation to temporal processes. Our finding might reflect the involvement of the amygdalo-hippocampal circuit in our task. Indeed, the hippocampus, a neighboring brain structure strongly connected to the amygdala, is considered critical in temporal processes, based on recent studies in rodents (Eichenbaum, 2013, 2014), in humans (Davachi and DuBrow, 2015), and computational models (Wallenstein et al., 1998). More specifically, previous research suggests a continuous interaction between the striatum and hippocampus in the seconds range (Jacobs

et al., 2013). Our VBM results are thus consistent with these studies.

In contrast with previous studies (Beste et al., 2007; Rao et al., 2014; Wild-Wall et al., 2008), Pre-HD participants performed as well as Controls in the present study. However, as argued above for HD patients, these studies are not purely based on production. For instance, the reproduction task used by Rao et al. (2014) also involves perception, as participants were first presented with a duration (in the range of seconds), and then had to reproduce that duration. The temporal deficit in Pre-HD participants here might thus be due to perception (Paulsen et al., 2004) and not production per se. The task used by Beste et al. (2007) and Wild-Wall et al. (2008) required participants to learn a specific duration through trial and error, given feedback after each attempt. Thus, the deficit found in Pre-HD participants in these studies may be explained by a difficulty with learning (which also involves the striatum, e.g. (Holl et al., 2012)) rather than a problem with temporal production.

In our data, temporal production variability correlated with most clinical scores, which were also largely correlated with each other. In order to better understand the structure of these correlations, we carried out an exploratory factor analysis, which highlighted 3 factors. The first factor was related to psychomotor and executive functions (with high loadings on TFC and motor scores but also on cognitive conflict as measured by the Stroop effect), the second was related to the generation of language (e.g. fluency tasks and the initiation sub-score of MDRS) and the third factor was associated specifically with memory abilities (with both immediate recall and delayed recall). Interestingly, amongst these three factors, temporal production performance was only correlated with the first factor. This result suggests that temporal production share functional processes with the psychomotor tasks. Such shared process may correspond to the motor aspect of the temporal production task. Indeed, in this task, participants not only need to estimate the temporal duration until a requested duration is reached, they also need to forward this estimation in real-time to motor control systems, in order to precisely control their movement and hit the keyboard at the requested time. In other words, the temporal production task is a motor timing task, unlike, e.g. tasks evaluating temporal perception where participants have to indicate which of two temporal durations is longest.

Finally, the deficit in temporal production observed here in HD patients is clinically relevant. Together with the difference between HD patients and Controls, the correlation between temporal production performance and the first factor (based on psychomotor clinical scores) pleads for considering temporal production as a good marker of Huntington's disease. Besides, the temporal production task has various advantages over conventionally used paper-and-pencil tests: it is fast, digitalized and independent of culture and language. Digitalized assessment improves standardization across sites and limiting potential investigator bias. Unlike other tasks for which deficits may depend heavily on language (e.g. Sumiyoshi et al., 2014) for issues with fluency tasks in schizophrenia), temporal production eliminates cultural and linguistic factors. This makes it easier to compare and combine results across countries, which is essential when setting up international projects. Moreover, our clinical impression is that this task does not put participants under much stress, as the task itself is simple to understand, and participants are not given negative feedback when they make errors, so they are not experiencing failures. Patients will therefore be accommodating to complete it. Yet, one limitation of this temporal production task is that it does not appear to be a good marker of the clinical evolution of the disease. Indeed, we do not find any degradation of the performance of HD patients on the temporal production task one year after the first session. It remains possible that our inability to detect a decline in temporal production over a year is due to the lower number of patients included at M12. Nonetheless, with the same number of observations, the clinical scores and VBM analyses seem capable to detect a deterioration of the striatum. This suggests that these tools are more appropriate to follow the decline of patients and place the temporal processing task as a detection task.

Credit author statement

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Laurie Lemoine, Marine Lunven, Nicolas Fraisse, Katia Youssov, Blanche Bapst, Graça Morgado and Vincent de Gardelle declare no conflict of interest.

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Data availability

The data that has been used is confidential.

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Appendix A. Supplementary data

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