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To cite this version:

Damien Bénis, Claire Haegelen, Philippe Voruz, Jordan Pierce, Valérie Milesi, et al.. Subthalamic nucleus oscillations during vocal emotion processing are dependent of the motor asymmetry of Parkinson's disease. NeuroImage, 2020, 222, pp.117215. 10.1016/j.neuroimage.2020.117215 . hal-02929529

HAL Id: hal-02929529

https://hal.science/hal-02929529v1

Submitted on 30 Sep 2020

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NeuroImage 222 (2020) 117215

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Subthalamic nucleus oscillations during vocal emotion processing are dependent of the motor asymmetry of Parkinson's disease

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ARTICLE INFO

Keywords:
Emotional prosody
Right hemisphere
Side of onset
Subthalamic nucleus
Parkinson's disease
Oscillations
Local-field potentials
Time-frequency
Theta, alpha, delta and gamma bands

ABSTRACT

The subthalamic nucleus (STN) is involved in different aspects of emotional processes and more specifically in emotional prosody recognition. Recent studies on the behavioral effects of deep brain stimulation (DBS) in patients with Parkinson's disease (PD) have uncovered an asymmetry in vocal emotion decoding in PD, with left-onset PD patients showing deficits for the processing of happy voices. Whether and how PD asymmetry affects STN electrophysiological responses to emotional prosody, however, remains unknown.

In the current study, local field potential activity was recorded from eight left- and six right-lateralized motor-onset PD patients (LOPD/ROPD) undergoing DBS electrodes implantation, while they listened to angry, happy and neutral voices.

Time-frequency decomposition revealed that theta (2–6 Hz), alpha (6–12 Hz) and gamma (60–150 Hz) band responses to emotion were mostly bilateral with a differential pattern of response according to patient's sides-of onset. Conversely, beta-band (12–20 Hz and 20–30 Hz) emotional responses were mostly lateralized in the left STN for both patient groups. Furthermore, STN theta, alpha and gamma band responses to happiness were either absent (theta band) or reduced (alpha and gamma band) in the most affected STN hemisphere (contralateral to the side-of onset), while a late low-beta band left STN happiness-specific response was present in ROPD patients and did not occur in LOPD patients.

Altogether, in this study, we demonstrate a complex pattern of oscillatory activity in the human STN in response to emotional voices and reveal a crucial influence of disease laterality on STN low-frequency oscillatory activity.

1. Introduction

The subthalamic nucleus (STN) has been shown to be involved in vocal emotion recognition by neuroimaging studies (Fruhholz et al., 2012; Péron et al., 2016), and impairments have been observed following disruption of STN functioning during deep brain stimulation (DBS) in patients with Parkinson's disease (PD) (Péron et al., 2015; J. 2010). Vocal emotion recognition includes processing of emotional prosody, which refers to changes in different segmental and supra-segmental aspects of voice such as rhythm and intonation that convey emotions during speech (Grandjean et al., 2005). For vocal emotion recognition in the cortex, Schirmer and Kotz proposed a model with sequential processing of the emotional percept in three steps (Schirmer and Kotz, 2006). First, an early acoustic analysis occurs in the auditory cortex from 0 to 150 ms post-utterance; second, the integration of emotionally significant acoustic cues occurs in the bilateral superior temporal gyrus (STG) and anterior superior temporal sulcus (STS) from 150 to 250 ms post-utterance; finally, the emotional information is made available for higher cognitive processes, taking place in the right inferior frontal gyrus (IFG) and orbitofrontal cortex (OFC) from 250 ms post-utterance. The investigation of the electrophysiological correlates of vocal emotion processing in the basal ganglia and more specifically in the STN, however, has only

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https://doi.org/10.1016/j.neuroimage.2020.117215
Received 27 March 2020; Received in revised form 2 July 2020; Accepted 27 July 2020
Available online 1 August 2020
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recently been a focus of interest in the literature and contains several discrepancies and open questions that need to be addressed.

In a recent study, Péron and collaborators (2017) reported the presence of an event related potential (ERP) in the right STN of PD patients that dissociated emotional (angry and happy) versus neutral voices from 300 to 400 ms post-sound onset (Péron et al., 2017). This type of study, however, does not address the dynamics of STN oscillatory activity in the time-frequency domain during the decoding of an emotional utterance. The only study, to date, using an STN power spectrum analysis of intraoperative multi-unit recordings in PD patients revealed a significant decrease of alpha and beta band activity during presentation of emotional onomatopoeia in the right ventro-medial part of the STN (Eitan et al., 2013). However, this study investigated the local activity of a small sample of neurons, in contrast with the investigation of the synchronized behavior of large neuronal populations in a given structure allowed by macro-electrode local-field potential (LFP) recordings. Furthermore, this study used onomatopoeia and did not investigate the correlates of emotional speech *per se*. Finally, the global spectrogram approach used in this study (Eitan et al., 2013) does not provide information about the time course of brain responses to emotion. This temporal information is crucial to understanding STN functioning as Péron and colleagues proposed that the STN could synchronize cortical and subcortical neural activity during emotion processing (Péron et al., 2013). From this model, we can infer that differential coordination of neural patterns, depending on the emotion component involved and the neural network modulated, could be implemented in the STN by oscillatory activity in different frequency bands. Each frequency band would then display different temporal dynamics and present modulations at different steps of the emotion decoding process.

Differential temporal dynamics of oscillatory activity during emotion processing has been suggested by electroencephalography (EEG) studies in the cortex (Chen et al., 2015; Y.-H. 2010; Giudice et al., 2016). One EEG study reported an early frontal and right temporal synchronization of theta band activity during angry voice presentation observed from 200 to 400 ms post-sound onset (Giudice et al., 2016), while another study reported a right anterior dissociation between anger and fear in the beta band from 300 to 500 ms post-sound onset (Jessen and Kotz, 2011). In the STN, presentation of emotional pictures also elicited an early theta and gamma band synchronization (around picture onset) followed by later beta (around 500 ms) and alpha (around 1000 ms) band desynchronizations (Huebl et al., 2014). Only alpha band activity, however, was modulated by the emotional content of the stimulus. It is then reasonable to assume that, as is the case for the visual modality, a differential temporal pattern of oscillatory activity across frequency bands could exist for emotional voices in the human STN. This could reflect a differential recruitment of brain networks in the different steps of emotional decoding predicted by the Schirmer and Kotz model (Schirmer and Kotz, 2006).

Another issue pending in the current literature is the apparent discrepancy between neuroimaging and electrophysiology on the matter of the laterality of the processing of emotional voices in the STN. While neuroimaging results in healthy controls consistently point toward a left lateralization of STN activity during emotion decoding (Fruhholz et al., 2012; Péron et al., 2016), electrophysiological studies in PD patients have found emotion-related ERP and low frequency band activity only in the right STN (Eitan et al., 2013; Péron et al., 2017). A possible hypothesis to explain this discrepancy involves the potential influence of PD asymmetry on the results from previous studies. Intracranial electrophysiological studies of the STN are by design performed on pathological populations (Eitan et al., 2013; Péron et al., 2017), whereas fMRI results for vocal emotion processing have been often obtained from healthy participants (Fruhholz et al., 2012; Péron et al., 2016, 2013). Recently, a stream of new evidence pointed toward a central influence of motor symptom asymmetry on the deficits in emotional prosody decoding observed in PD patients (Garrido-Vásquez et al., 2013; Stirnimann et al., 2018; Ventura et al., 2012). These deficits were shown to affect specifically left-onset PD patients (i.e. patients where the left side of the body was the most affected by motor symptoms; LOPD) whereas right-onset PD patients (ROPD) performed similarly to healthy controls (Garrido-Vásquez et al., 2013; Stirnimann et al., 2018; Ventura et al., 2012). Contributions of specific emotions to these deficits were heterogeneous between studies: a specific deficit in LOPD patients in happiness (Stirnimann et al., 2018) or sadness recognition (Ventura et al., 2012) has been reported. These LOPD-specific impairments also were correlated with a metabolism decrease in the right OFC (Stirnimann et al., 2018) and a reduction in the frontal ERP P200 responses to emotional voices (Garrido-Vásquez et al., 2013). This suggests a specific role of the right basal-ganglia-OFC pathway in the deficits in emotional prosody decoding observed in PD. PD asymmetry seems, then, to have a drastic impact on emotional prosody recognition (Stirnimann et al., 2018; Ventura et al., 2012) and on the electrophysiological correlates of this process in the cortex (Garrido-Vásquez et al., 2013). Yet a close inspection of the two intracranial STN studies investigating emotional prosody decoding reveals an unbalanced design concerning PD asymmetry. Eitan et al. (2013) study featured 10 LOPD patients out of 17 while Péron et al. (2017)'s study featured an almost 2:1 ratio in favor of LOPD patients (i.e. the patients farthest from healthy physiological functioning in terms of emotional prosody decoding) (Stirnimann et al., 2018; Ventura et al., 2012).

Therefore, to fully address this issue and as a follow-up to the Péron et al., 2017 study, the current study investigated the effect of PD side of onset on lateralized STN activity in the time-frequency domain during emotional prosody decoding. We aimed in this study to investigate the temporal dynamics in different frequency bands of STN LFP activity, and the influence of PD side of onset on these spectral modulations in each hemisphere. Specifically, time-frequency decomposition was performed on the left and right STN activity recorded in LOPD and ROPD patients in the course of their implantation with DBS electrodes while they listened to meaningless human emotional voices (angry, happy, and neutral). We present results showing differential effects of PD side of onset and hemispheric lateralization on STN oscillatory response to emotional voices in different frequency bands.

2. Materials and methods

2.1. Patients (Table 1)

The electrophysiological data was obtained from 14 PD patients (six male, eight female), 11 already included in the ERP study by Péron et al., 2017 to which were added three additional patients that were included following this previous publication. Clinical details of the patients are described in Table 1. They were selected for their capacity and readiness to participate in a demanding cognitive task. They were undergoing STN implantation of DBS electrodes at Rennes University Hospital (France) using standard surgical procedure (Péron et al., 2017). Patients were in conformity with standard inclusion criteria for DBS surgery at the time of the inclusion (Péron et al., 2017; Table 1, SI Appendix). PD motor symptoms started on the left side of the body for eight patients (LOPD), and on the right side of the body for six patients (ROPD).

To further characterize PD asymmetry at the time of the recording, we computed for each patient an asymmetry index from the lateralized items (Items 20–26) of Part III of the Unified Parkinson's Disease Rating Scale by subtracting the item scores related to the left side of the body from the item scores related to the right side of the body (Table 1, Stirnimann et al., 2018; Voruz et al., 2020). Patient asymmetry indexes were consistent with their reported side of onset, except for one ROPD patient whose disease lateralization evolved toward a mostly bilateral but slightly left-leaning asymmetry.

The study was approved by the ethics committee of Rennes University Hospital (approval number IDRCB: 2011-A00392–39) and all patients gave their written informed consent to participate in this study.

Table 1
Clinical characteristics of included patients. SCL = Socio-cultural level, *L*=Left, *R*= Right, Eq-DOPA= *L*-DOPA equivalent.

ID	*Sex*	*Age*	*SCL (year)*	*Side of Onset*	*Asymetry Index*	*Disease's Duration (year)*	*L-DOPA Daily dose (Eq-DOPA)*	*UPDRS3 off DOPA*	*UPDRS3 on Dopa*	*MDRS*	*Stroop I*	*TMT B-A*	*MCST C*	*MCST E*	*MCST P*	*MADRS*	*AES*
1	F	61	12	L	−2	5	2057.5	32	8	144	4.62	26	4	15	5	3	23
2	F	54	6	R	−1.5	15	400	53	18	139	−14.73	102	3	19	5	20	48
3	F	63	12	R	3.5	7	650	36	17	144	13.36	47	6	7	3	5	37
4	M	61	14	L	−6	8	1450	48	22	136	1.06	86	6	4	1	0	23
5	M	53	14	L	−6.5	6	1740	41	17	138	−12.52	NC	6	0	0	10	25
6	M	61	6	R	2.5	6	1887.5	28	6	141	−2.17	24	6	5	3	5	34
7	F	46	12	L	−10	10	300	25	7	134	−1.67	31	6	2	0	1	34
8	F	55	9	L	−8.5	9	1150	55	30	142	−4.40	40	6	1	1	1	33
9	M	50	14	L	−14.5	7	637.5	34	8	144	2.29	13	6	2	0	0	26
10	M	43	14	R	4	9	100	31	3	137	3.37	35	6	4	0	3	24
11	M	52	15	L	−1.5	4	375	52	24	142	5.56	33	6	0	0	14	46
12	F	58	7	L	−3	10	715	48	19	143	1.82	NC	5.8	9	4	3	29
13	F	43	6	R	10	11	410	NC	NC	141	7.04	38	6	0	0	8	27
14	F	50	10	R	2	8	1517.5	30	11	141	−1.59	31	6	0	0	8	33

2.2. Electrode implantation and local field potential recordings

Following DBS electrode implantation in the STN (Medtronic model 3389) using a standard clinical procedure (Benabid et al., 2009, 2005), data were obtained at the patient's bedside two days postoperatively from four adjacent contacts of the DBS electrode (0, 1, 2, and 3, contact 0 being the most distal contact), amplified, and sampled at a common rate of 1000 Hz. Patients subthalamic LFP signals were recorded on their usual therapeutic medication. One patient was implanted unilaterally (left STN). More details are available in SI Appendix.

2.3. Experimental procedure

This study used data previously acquired for the Péron et al. (2017) study and completed as already mentioned above, and a detailed description of the one-back task and stimuli used can be found in Péron et al., 2017. Meaningless vocal stimuli expressing anger, happiness or neutral prosody were presented through in-ear stereo headphones (Sennheiser, CX 2.00) in a pseudorandomized order. All the sounds were matched for mean energy, counterbalanced for gender and the sentence pronounced, and mean duration did not differ significantly between the three conditions (one-way analysis of variance, $F_{(2,10)}$=0.1905, p = 0.8271, BF10 =0.155). A behavioral test performed on nine of the included patients confirmed that the emotional content of these stimuli was accurately recognized by participants (see SI Appendix). Participants performed one to three blocks of 60 emotion trials in each block (20 trials for each emotional voice condition [angry, happy and neutral]). Each sound was preceded by a pseudorandom fixation period (50–250 ms) and followed by a pseudorandom jitter (50–500 ms) and a silent period (2.95 s duration). Participants were instructed to stay focused on these auditory stimuli and to press a button whenever they heard two identical stimuli in a row. One-back trials with motor responses represented only 10% of the total trials and were excluded from the LFP analyses. More details on the stimuli and the task used can be found in SI Appendix and Péron et al., 2017.

2.4. Data analysis

The electrophysiological analyses were performed using SPM (http://www.fil.ion.ucl.ac.uk/spm/), Fieldtrip (http://www.fieldtriptoolbox.org/) toolboxes for MATLAB and custom Matlab functions. Data is available to readers upon request to the corresponding author.

2.4.1. Bipolar montage

The electrophysiological data was analyzed using a sequential bipolar montage applied offline, giving a total of three channels per STN side (0–1, 1–2 and 2–3, 0 being the most ventral contact). We selected the most ventral contact (0–1) on each STN side for subsequent analysis, as postoperative CT scans showed that these contacts were located within the STN (Péron et al., 2017).

2.4.2. Event-related-potential (ERP) analysis

Following the Péron et al., 2017 study, an ERP analysis (n = 14) was performed using a method previously described (Péron et al., 2017). After epoching (1.25 s before sound onset to 3.7 s post-sound onset), and artifact rejection (see SI Appendix), LFP signals from each trial were filtered offline with a 0.1–30 Hz bandpass FIR filter for this ERP analysis. A baseline correction was then applied for each trial, using the 1 s time interval in the silent period preceding the fixation cross. Average event-related activity was then obtained by averaging all trials from a given condition together (anger, happiness, neutral) from the right and left STN, from LOPD and ROPD patients separately. Significant ERP differences between emotional and neutral voices were computed using a Montecarlo test. To take into account that the epochs are measured on different patients, we modified the Fieldtrip function so that permutations occurred only within participants, in accordance with the principle that only similar epochs can be permuted (more details can be found in Péron et al., 2017). P-values from all conditions were corrected for multiple comparison using the cluster-based comparison method implemented in the Fieldtrip toolbox (p<0.05).

2.4.3. Time-frequency decomposition procedure

After epoching (1.25 s before sound onset to 3.7 s post-sound onset) and artifact rejection, two analysis steps were performed for each condition on LOPD and ROPD patients in the right and left STN separately.

First, a standard time-frequency decomposition procedure (Bosman et al., 2012) was performed separately for high (40–150 Hz, multitaper) and low-frequency responses (2–40 Hz, hanning single taper) as higher frequencies require a larger bandwidth and are better estimated using a multitaper approach (Mitra and Pesaran, 1999). For low frequency response (2–40 Hz), LFP activity in an adaptative time window (6 cycles/frequency, from 1.25 s before stimulus to 3.7 s after stimulus in steps of 50 ms) was convolved using a Hanning window and multiplied by complex exponentials at frequencies for 2 to 40 Hz with a logarithmically spaced step. For high frequency responses (40–150 Hz), LFP activity in a 400 ms time window (from 0.25 s before stimulus to 3.7 s after stimulus in steps of 50 ms) was convolved using seven discrete slepian tapers and multiplied by complex exponentials at frequencies for 40 to 150 Hz with a logarithmically spaced step (with an effective smoothing of 10 Hz in both directions). A baseline correction was then applied for each trial, using the 1 s time interval in the silent period preceding the fixation.

Second, a nonparametric Montecarlo permutation test was performed for each condition relative to baseline, on the whole trial pool using the modified procedure described above (see ERP analysis) from 0.25 s before sound onset to 3.7 s post-sound onset. The fixation period was included in this analysis to account for potential low-frequency spectral leakage issues, as well as expectancy effects due to presentation of the fixation cross. P-values were corrected using FDR. This analysis allowed us to delineate frequency bands of interest (significantly modulated by experimental conditions) for further time-course analysis. To estimate more precisely the time-course of oscillatory STN responses in frequency bands of interest, we extracted for each trial the average oscillatory power within defined frequency bands of interest. Single trial oscillatory power extracted for each emotional condition (angry, happy, neutral voice), from the left and right STN in LOPD and ROPD patients were compiled into a single database for each frequency band considered. We then ran a two-step general linear mixed model analysis to address the following experimental questions (see also Introduction).

2.4.4. General linear mixed model analysis

This analysis aimed at addressing the following questions: is STN oscillatory time course activity in each frequency band selectively modulated by angry, happy and neutral voices, and is this oscillatory time course activity influenced by hemispheric laterality of the recording site and PD side of onset? We assessed whether each frequency band of interest was able to dissociate angry, happy and neutral voice presentation in both STN in both patient groups. To this end, power in each frequency band was computed for each trial in 100 ms bins using a sliding window with a 50 ms step from the sound-onset to 3.7 s post-sound onset. This data, upon confirmation of its normal distribution, was entered into a two-step general linear mixed model approach. Firstly, a "classical" general linear mixed model (GLMM) approach, using the lmer R package, was implemented. This approach provides an accurate estimation of the contribution of task-related factors over confounding variables, entered as random factors. At each of the 73 time bins (100 ms wide), oscillatory power in a given frequency band was entered as dependent variable, whereas Condition (three levels, Angry, Happy and Neutral), Hemisphere (two levels, Left and Right STN) and PD Side of onset (two levels, LOPD and ROPD) were entered as fixed factors. Sex, patient code

(14 levels) and the gender of the emotional stimulus were entered as random factors, following a selection method using the Aikake Information Criteria (AIC) and Bayesian Information Criteria (BIC) that assessed their critical contribution to the variance in the model. We then computed for each 73 bins the main effect of Condition (whether oscillatory power is influenced by emotion independently from laterality and side of onset), two-way interaction of Condition x Side of onset and Condition x Hemisphere testing the influence of each factor on the processing of emotional voices as well as the three-way interaction Condition x Side of onset x Hemisphere. Then, at each time bin, in line with our hypothesis of a differential hemispheric lateralization and effect of side-of -onset according to the frequency band considered, planned contrasts were performed in each model 1) between each condition for each STN side in LOPD and ROPD, 2) between left and right STN for each condition in LOPD and ROPD patients and 3) between LOPD and ROPD patients for each STN side for each condition. All p-values from the model and the contrasts were corrected for multiple comparison using an FDR approach (Benjamini and Hochberg, 1995).

Secondly, a Bayesian general linear mixed model approach was used, through the R "BayesFactor" package (Morey and Rouder, 2011, SI Appendix: Bayesian Model 1). This approach computed an index of the relative Bayesian likelihood of a H_1 model compared to the H_0 model. Consequently, the Bayes Factor computed by this method allows the assessment of the null hypothesis. Indeed, while a Bayes Factor>3 indicate a substantial proof of the H_1 hypothesis, a Bayes factor <1/3 is a substantial proof of the H_0 hypothesis. Furthermore, the Bayes Factor allows to directly assess the strength of the proof for either the H_1 or the null hypothesis (a strong proof is linked to a Bayes Factor within the [10 30] or [1/10 1/30] boundaries, while an extreme proof is linked to a Bayes Factor>100 or <1/100). Finally, the comparative nature of Bayesian GLMM makes it unsusceptible to multiple comparison. We used the same parameters in this analysis as the ones used in the classical GLM approach and the same main effects, interaction effects and contrasts were computed using this approach. We considered an effect to be significant if both approaches yielded consistent significant results.

A happiness-specific effect is a time period where we observed a significant dissociation between happy voices and angry voices as well as a significant dissociation between happy voices and neutral voices. An anger-specific effect is a time period where we observed a significant dissociation between angry voices and happy voices as well as a significant dissociation between angry voices and neutral voices. An emotion-specific effect is a time period where we observed a significant dissociation between angry voices and neutral voices as well as a significant dissociation between happy voices and neutral voices.

2.4.5. Effect of PD asymmetry on STN responses to emotion

Because the patients included in the current study displayed an extended range of asymmetry indexes, indicating heterogeneity in PD asymmetry, we performed a complementary analysis. Its goal was to control for the linear influence of PD asymmetry on the specific effects of emotional voices observed in our main analysis. For each significant effect of emotional voices observed in the main time-frequency analysis, we computed a database subset that included the time period and STN side for which the considered effect was observed. Then, we computed, using each database, the main effect of the asymmetry index (continuous variable, range [−14.5 10]) and the Asymmetry Index × Condition (three levels: angry, happy, neutral) two-way interaction on power by using a classic GLMM. Patient was entered as a random factor. Contrast analysis was then performed on the two-way interaction by using the R package emtrends function to test, for each condition, the significance of the linear correlation between power and the asymmetry index, as well as the significance of power versus the asymmetry index trend differences between emotional vocal conditions. A similar analysis was performed on the event-related potential scale (by using subsets of a database with average power in 50 ms bins from 0 to 3.7 s post-sound onset).

3. Results

In the one-back task, patients responded accurately in 76.62 ± 15.76% of one-back trials. Incorrect responses to non-one-back trials (false alarm) accounted for 1.53 ± 2.35% of the total trial count. These contaminated trials were not included in electrophysiological analysis (see methods). No behavioral differences were detected between LOPD and ROPD patients in terms of successful one-back trials ($t_{(1)}$=0.012, p = 0.99) and false-alarms ($t_{(1)}$=0.058, p = 0.95) .

27 STN contacts from eight LOPD and six ROPD patients (seven left STN and eight right STN for LOPD, six left STN and six right STN for ROPD patients) were analyzed in order to evaluate the pattern of oscillatory activity in different frequency bands during presentation of angry, happy and neutral voices.

3.1. Event-related potential analysis (Fig. 1)

The ERP analysis revealed a strong effect of the patient's side of onset.

LOPD patients. A dissociation in the *left STN* between angry and neutral voices was observed from 429 ms to 462 ms post-sound-onset (PSO) (cluster-statistic=−87.77, p = 0.012) and between happy and neutral voices from 415 ms to 448 ms PSO (cluster-statistic=−93.37, p = 0.006). In the *right STN*, a biphasic dissociation was observed between angry and neutral voices 220 ms to 283 ms (cluster-statistic=168.3, p = 0.003) and 2760 ms to 2808 ms PSO (cluster-statistic=127.9, p = 0.02), and between happy and neutral voices from 232 to 291 ms (cluster-statistic=16.1, p = 0.003) and 3285 to 3325 ms PSO (cluster-statistic=132.57, p = 0.0163).

ROPD patients. In ROPD patients, a single late happiness versus neutral dissociation occurred in the *right STN* from 3427 to 3440 ms PSO (cluster-statistic=38.59, p = 0.024).

3.2. Time frequency pattern

Time frequency decomposition revealed that, overall, voices onset was followed by a theta band (2–6 Hz) event-related synchronization (ERS), and an alpha (6–12 Hz) and beta band (12–20 Hz and 20–30 Hz) desynchronization (ERD) compared to baseline (see SI appendix Figure S1).

A close inspection of the time course of activity in each frequency band in the STN revealed three main patterns regarding the influence of the PD side of onset and STN laterality. We will discuss these three-patterns in the following paragraphs.

3.3. A low-frequency oscillatory response to emotional voices strongly influenced by PD side of onset (Fig. 2)

Overall, oscillatory activity within low frequency bands (theta and alpha band) was significantly influenced by the side-of onset of the patients (Fig. 2), as evidenced by a global Condition x Side of onset two-way interaction at 300–400 ms, 1700–2600 ms, and 2800–3250 ms PSO for theta band activity, and at 0–650 ms, 750–1600 ms, and 1650–2600 ms and 2850–3550 ms PSO for alpha band activity (Table 3, p <0.05, BF_{10}>3).

In the theta band, LOPD patients displayed an emotion-specific ERS in the left STN (400–1100 ms PSO) and an earlier anger-specific ERS in the right STN (Fig. 2A, 200–450 ms PSO, Table 2, p <0.05, BF_{10}>3). ROPD patients, on the other hand, displayed a significant happiness-specific ERS in the left STN (800–950 ms PSO) and the right STN (600–1400 ms PSO), followed by a significant anger-specific ERD (1850–2450 ms and 2850–3100 ms PSO, Table 2, p <0.05, BF_{10}>3).

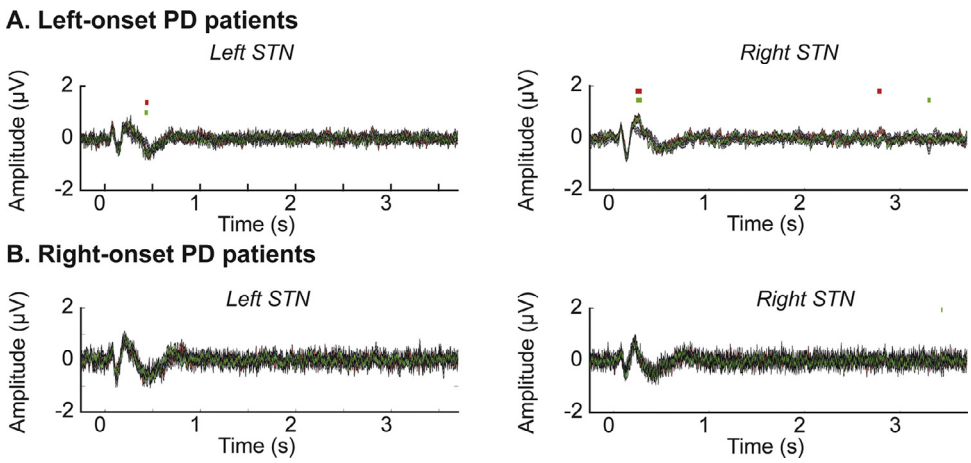

Fig. 1. STN event-related activity during presentation of emotional voices for A. LOPD and B. ROPD patients in the left and right STN for anger, neutral and happiness. 0 ms represents the onset of the sound in panels and shaded areas indicate ±1 standard error. Horizontal lines represent the time periods when a significant contrast between conditions was revealed by Montecarlo test (p <0.05 cluster-based comparison corrected). Green lines = happy voices vs neutral voices contrasts; red lines = angry voices vs neutral voices contrasts.

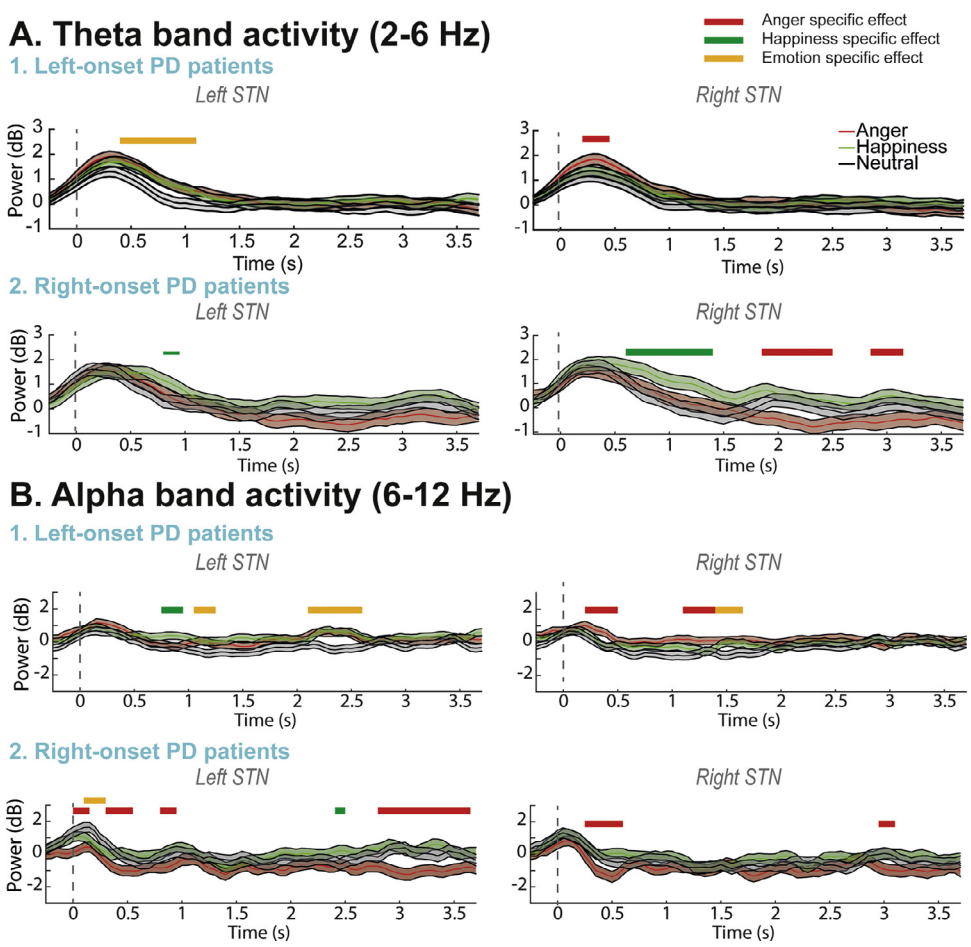

Fig. 2. STN oscillatory activity time course in the low-frequency bands, (A) theta band (2–6 Hz) and (B) alpha band (6–12 Hz), during presentation of emotional voices. A-B. Average time course of STN oscillatory activity for LOPD (1) and ROPD patients (2) in the left (left column) and right (right column) STN, during angry voices (red), happy voices (green) and neutral voices (black). A-B: 0 ms represents the onset of the sound in panels and shaded areas indicate ±1 standard error. Thick horizontal lines represent the time periods when a significant contrast between conditions was revealed by classical and Bayesian analyses. Thin lines represent contrasts that were significant in the Bayesian analysis, but only reached trend level in the classical GLMM approach. Red lines represent a significant anger-specific contrast. Green lines represent a significant happiness specific-contrast. Yellow lines represent a significant emotion-specific contrast.

In the alpha band, LOPD patients displayed an early happiness-specific ERS in the left STN (750–950 ms PSO) followed by a later emotion-specific ERS (1050–1250 ms and 2100–2600 ms PSO, Table 2, p <0.05, BF_{10}>3). In the right STN, they also exhibited an anger-specific ERS (200–500 ms and 1100–1400 ms PSO) followed by a later emotion-specific ERS (Fig. 2B, 1400–1650 ms PSO, Table 2, p <0.05, BF_{10}>3). ROPD patients displayed a significant bilateral anger-specific ERD (Fig. 2B, early component: 0–150 ms, 300–550 ms and 800–950 ms PSO in the left STN, 250–600 ms PSO in the right STN; late component: 2800–3650 ms PSO in the left STN, 2950–3100 ms PSO in the right STN). There was also a significant emotion-specific ERS at 100–300 ms PSO and a happiness-specific ERS at 2400–2500 ms PSO in the left STN (Table 2, p <0.05, BF_{10}>3).

Interestingly, planned contrast comparison between left and right STN responses (through classical and Bayesian contrast analysis in line with our hypotheses, see methods) showed significant hemispheric differences for the responses to happiness. Indeed, a significantly higher theta power for happiness was observed from 1150 to 1250 ms PSO in the right STN compared to the left STN in the ROPD group (Table 3, BF_{10}>3). Furthermore, a significantly higher alpha power for happiness was observed from 300 to 1000 ms, 1300–1400 ms, 1750–2000 ms, and 2100–2550 ms PSO in the left STN compared to the right STN in the

Table 2
Significant dissociations between conditions for all frequency bands. ERS= Event-related synchronization, ERD= Event-related desynchronization. In the Effects column, EMO= Emotion specific, ANG= Anger-specific, HAP=Happiness-Specific. Contrasts reported are ANG-HAP= Angry versus Happy voices, ANG-NEU= Angry versus Neutral voices, HAP-NEU= Happy versus Neutral voices. For significant contrasts, the minimum BF_{10} is reported, along with the significance in the designated interval of the contrast in the classical analysis (*: max p-value in the interval<0.05; ***: max p-value in the interval<0.01), as well as the temporal range of strong Bayesian GLMM effects (BF_{10}>100).

Frequency	Condition	Effect	Timing(ms)	ANG-NEU		HAP-NEU		ANG-HAP	
				Effect	BF10>100	Effect	BF10>100	Effect	BF10>100
Left-onset PD patients									
Left STN									
2–6 Hz	EMO	ERS	400–1100	18,5*	500–950	4,76*	650-900	<1/3	N.A
6–12 Hz	HAP	ERS	750–950	<1/3	N.A	64,88***	N.A	7,10***	N.A
	EMO	ERS	1050–1250	10,19***	N.A	28,8***	N.A	<1/3	N.A
	EMO	ERS	2100–2600	18,7***	2150–2550	4,63*	2150–2600	<1/3	N.A
12–20 Hz	HAP	ERS	1050–1200	<1/3	N.A	15,88*	N.A	93,6***	N.A
	EMO	ERS	1500–1600	197.96*	N.A	4.58	N.A	<1/3	N.A
60–150 Hz	ANG	ERS	2900–3200	47,04*	N.A	<1/3	N.A	51,95*	2900–3100
	ANG	ERS	3350–3450	24.54*	N.A	0.06	N.A	3.4	N.A
Right STN									
2–6 Hz	ANG	ERS	200–450	97,92***	250 450	<1/3	N.A	4,26*	N.A
6–12 Hz	ANG	ERS	200–500	17,69***	250–450	<1/3	N.A	4,1*	300–450
	ANG	ERS	1100–1400	14,49***	1100–1250	<1/3	N.A	3,7*	N.A
	EMO	ERS	1400–1650	222,46***	1400–1650	4,35*	N.A	<1/3	N.A
30–40 Hz	HAP	ERD	200–300	0.053	N.A	18.17*	N.A	4.88	N.A
Right-onset PD patients									
Left STN									
2–6 Hz	HAP	ERS	800–950	<1/3	N.A	29,64*	800–900	3,68	N.A
6–12 Hz	ANG	ERD	0–150	1.7E4***	0–150	0,22	N.A	4,29*	N.A
	EMO	ERD	100–300	3425*	100–300	5,86*	N.A	0,27	N.A
	ANG	ERD	300–550	4,97*	300–450	0,07	N.A	3,62*	N.A
	ANG	ERD	800–950	4,45*	N.A	<1/3	N.A	77***	850–950
	HAP	ERS	2400–2500	<1/3	N.A	3.41***	N.A	24***	N.A
	ANG	ERD	2800–3650	4,35*	2850–3200 3400–3550	0,05	N.A	18***	2800–3550
12–20 Hz	HAP	ERS	850–1000	0.04	900–1000	42,5*	N.A	106***	850–1000
	HAP	ERS	2250–2400	<1/3	N.A	48,12*	N.A	4,93	N.A
20–30 Hz	EMO	ERS	2100–2200	28.92*	N.A	3.64	N.A	<1/3	N.A
30–40 Hz	ANG	ERD	1200–1300	202.47*	1200–1300	0.067	N.A	763*	1200–1300
60–150 Hz	ANG	ERD	450–550	7.48*	N.A	0.073	N.A	3*	N.A
	ANG	ERD	1950–2150	13.43*	1950–2050	<1/3	N.A	6*	N.A
Right STN									
2–6 Hz	HAP	ERS	600–1400	<1/3	N.A	7,96*	700–850 1000–1400	4,7 *	N.A
	ANG	ERD	1850–2450	10,49*	2200–2300	<1/3		2721***	1850–2450
	ANG	ERD	2850–3100	3,83*	N.A	<1/3		435***	2850–3100
6–12 Hz	ANG	ERD	250–600	3,56*	N.A	0,063	250–550	8***	350–600
	ANG	ERD	2950–3100	12,4***	N.A	<1/3		25***	N.A
12–20 Hz	HAP	ERD	1900–2000	1.48	N.A	9.4E4*		4.394	N.A
60–150 Hz	HAP	ERS	200–650	<1/3	N.A	3.24***		14***	350–650
	ANG	ERD	700–1050	9.17*	350–650	0.06		18***	700–1050

LOPD group (Table 3, BF_{10} >3). Along with the abolition of the theta ERS for happiness observed in the right STN of LOPD patients (where only an anger-specific ERS is observed), these results seem to point, in these low frequency bands, toward a reduction of STN responses to happiness in the STN contralateral to the side of onset of PD patients.

3.4. Left-lateralized beta-range oscillatory response to emotional voices (Fig. 3)

High and low beta frequency band activity showed emotional modulations lateralized to the left STN (Fig. 3, SI appendix and Figure S3). A combined effect of PD side of onset and hemispheric recording site was evident in the three-way Condition x Side of onset x Hemisphere interaction from 1500 to 1650 ms PSO for low-beta activity only (Table 3, p <0.05, BF_{10}>3).

Indeed, in the low-beta band, a significant left STN ERS was observed for happy voices in ROPD patients (850–1000 ms PSO) and LOPD patients (1050–1200 ms PSO, Fig. 3, Table 2, p <0.05, BF_{10}>3). Note that for both patient groups, no dissociation between happiness and other conditions was present in the right STN in the same time period (850–1200 ms, BF_{10}<1/3); this lateralization effect was confirmed by a significant difference for happiness between left and right STN in the ROPD group during the early component of the happiness−specific effect (800−1050 ms PSO, Table 3, p <0.05, BF_{10}>3). Note that Bayesian analysis indicated emotion-specific dissociations at a later timing (although the classical analysis was trending for one of the contrasts of interest, Table 2, Fig. 3). These dissociations included a later happiness-specific component in the left STN of ROPD (2250–2400 ms PSO), a short left STN maintenance of a higher beta power for emotional voices in LOPD patients (1500–1600 ms PSO), and a late right STN ERD for happiness (1900–2000 ms PSO) in ROPD patients.

These results point toward a mainly left lateralization of STN beta band activity, and a reduction of late emotional beta modulations in LOPD patients compared to ROPD patients.

Table 3
Significant laterality effects (Left STN > right STN) for all frequency bands. For significant contrasts, the minimal BF_{10} values on the time-interval of the effect along with the significance level of the classical analysis (*: max p-value in the interval<0.05; ***: max *p*–value in the interval<0.01) are reported as well as the temporal range of strong Bayesian GLMM effects (BF_{10}>100). Effects: EMO X SIDEONSET= two-way interaction effect of the emotion of the voices (anger, happiness, neutral) and the side-of-onset of the patient (LOPD and ROPD); EMO X HEMI = two-way interaction effect of the emotion of the voices and STN hemisphere (left and right STN); EMO X SIDEONSET X HEMI = three-way interaction effect of the emotion of the voices, the side-of-onset of the patient and STN hemisphere. Other effects reported come from GLMM contrasts between left and right STN for the condition of interest (CONDITION column).

Frequency	CONDITION	Side-of-Onset	EFFECT	Timing (ms)	Significance (minBF_{10})	BF_{10}>100 (timing, ms)
2–6 Hz	ALL	ALL	EMO X SIDEONSET	300–400	4.31***	N.A
	ALL	ALL	EMO X SIDEONSET	1700–2600	5,37***	1800–2100
	ALL	ALL	EMO X SIDEONSET	2800–3250	3*	N.A
	HAP	ROPD	Left < Right STN	1150–1250	3.23*	N.A
6–12 Hz	ALL	ALL	EMO X SIDEONSET	0–650	67,43***	0–600
	ALL	ALL	EMO X SIDEONSET	750–1600	5,04***	850–1150 1350–1550
	ALL	ALL	EMO X SIDEONSET	1650–2600	6,60***	1750–1950 2200–2450
	ALL	ALL	EMO X SIDEONSET	2850–3550	3,76***	2900–3300 3350–3500
	HAP	LOPD	Left > Right STN	300–1000	9,36*	800–900
	HAP	LOPD	Left > Right STN	1300–1400	6.41*	N.A
	HAP	LOPD	Left > Right STN	1750–2000	3.03*	N.A
	HAP	LOPD	Left > Right STN	2100–2550	8,9 *	2150–2400
	NEU	LOPD	Left > Right STN	250–700	3,44 *	N.A
12–20 Hz	ALL	ALL	EMO X SIDEONSET X HEMI	1500–1650	3,38*	N.A
	ALL	ALL	EMO X SIDEONSET	1850–2000	15,37*	N.A
	ALL	ALL	EMO X SIDEONSET	2800–2950	8,5*	N.A
	ALL	ALL	EMO X LAT	1750–1900	3.74*	N.A
	HAP	LOPD	Left > Right STN	50–200	35,26 *	N.A
	HAP	ROPD	Left > Right STN	800–1050	25,66*	N.A
	NEU	LOPD	Left < Right STN	1500–1600	4.46*	N.A
	NEU	LOPD	Left < Right STN	1750–1850	6.19*	N.A
20–30 Hz	ANG	LOPD	Left < Right STN	2250–2350	16.67*	N.A
	HAP	ROPD	Left > Right STN	0–400	122,52*	0–400
	HAP	ROPD	Left > Right STN	900–1000	33.9*	N.A
	NEU	LOPD	Left > Right STN	50–150	84.08*	N.A
	NEU	ROPD	Left > Right STN	150–350	21,219*	150–300
30–40 Hz	ALL	ALL	EMO X HEMI	300–400	13.84*	N.A
	HAP	ROPD	Left > Right STN	50–150	765.9*	N.A
	NEU	LOPD	Left < Right STN	3100–3250	126*	N.A
60–150 Hz	ALL	ALL	EMO X SIDEONSET	100–1100	3.57*	300–950
	ALL	ALL	EMO X SIDEONSET	1700–2350	3.4*	1900–2250
	HAP	ROPD	Left < Right STN	400–650	6.637*	N.A
	HAP	ROPD	Left < Right STN	1750–1900	3.83***	N.A
	NEU	LOPD	Left < Right STN	2300–2550	10.96*	N.A
	NEU	LOPD	Left < Right STN	2700–3050	10.9*	2900–3000

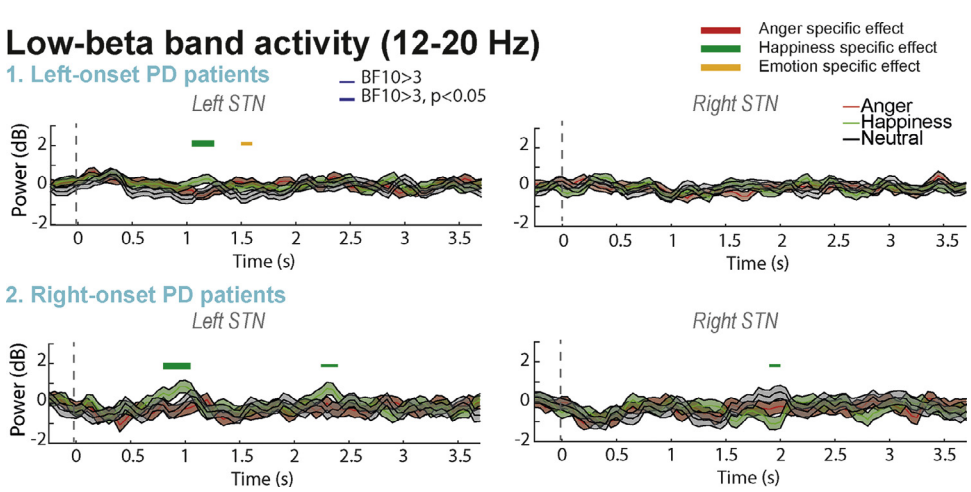

Fig. 3. STN oscillatory activity time course in the low-beta band (12–20 Hz) during presentation of emotional voices. Average time course of STN oscillatory activity for LOPD (1) and ROPD patients (2) in the left (left column) and right (right column) STN, during angry voices (red), happy voices (green) and neutral voices (black). 0 ms represents the onset of the sound and shaded areas indicate ±1 standard error. Thick horizontal lines represent the time periods when a significant contrast between conditions was revealed by classical and Bayesian analyses. Thin lines represent contrasts that were significant in the Bayesian analysis, but only reached trend level in the classical GLMM approach. Red lines represent a significant anger-specific contrast. Green lines represent a significant happiness-specific contrast. Yellow lines represent a significant emotion-specific contrast.

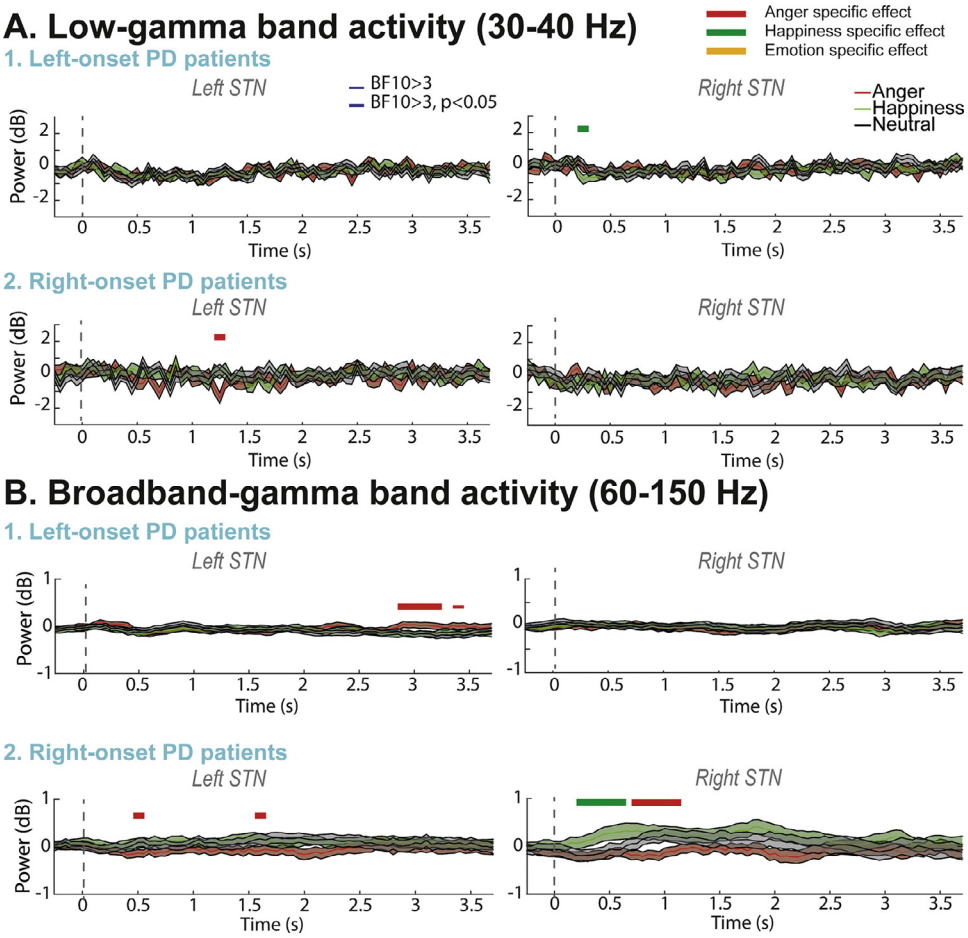

Fig. 4. STN oscillatory activity time course in the (A) low-gamma (30–40 Hz) and (B) broadband-gamma (60–150 Hz) bands during presentation of emotional voices. A-B. Average time course of STN oscillatory activity for LOPD (1) and ROPD patients (2) in the left (left column) and right (right column) STN, during angry voices (red), happy voices (green) and neutral voices (black). 0 ms represents the onset of the sound in panels and shaded areas indicate ±1 standard error. Thick horizontal lines represent the time periods when a significant contrast between conditions was revealed by classical and Bayesian analyses. Thin lines represent contrasts that were significant in the Bayesian analysis, but only reached trend level in the classical GLMM approach. Red lines represent a significant anger-specific contrast. Green lines represent a significant happiness-specific contrast. Yellow lines represent a significant emotion-specific contrast.

3.5. Gamma-range oscillatory response to emotional voices: under both factors' influence? (Fig. 4)

Finally, gamma frequency band activity presented a particular pattern of response (Fig. 4).

Low-gamma activity was predominantly lateralized (Condition x Hemisphere interaction from 300 to 400 ms PSO, Table 3, $BF_{10}>3$, $p<0.05$) and the Bayesian analysis suggested an effect of the PD side of onset as well (Condition x Side of onset x Hemisphere interaction from 1800 to 1900 ms PSO, $BF_{10}=5.42$, $p = 0.056$). In the low−gamma band, ROPD patients displayed, in the left STN, a significant anger−specific gamma ERD from 1200 to 1300 ms PSO while LOPD patients presented a short happiness-specific low-gamma ERD in the right STN from 200 to 300 ms (Table 2, $p<0.05$, $BF_{10}>3$). Additionally, a late low-gamma ERS for neutral voices in the right STN of LOPD patients was suggested by the Bayesian analysis (Fig.S4, 3100–3200 ms PSO, anger vs. neutral, $BF_{10}=8.17$, happiness vs. neutral, $BF_{10}=3.536$), and is in coherence with the observation of a significantly higher low-gamma power during this time period for neutral voices in the right compared to the left STN (Table 3, $p<0.05$, $BF_{10}>100$).

In the broadband-gamma band, a strong effect of PD side of onset was observed along the trial length (Condition x Side of onset interaction, 100–1100 ms and 1700–2350 ms PSO, Table 3, $BF_{10}>3$, $p<0.05$). LOPD patients presented a late anger−specific ERS in the left STN (2900–3200 ms PSO, Table 2). On the other hand, ROPD patients presented a strong happiness−specific gamma ERS in the right STN (200–650 ms PSO) followed an anger-specific ERD (750–1050 ms PSO, Table 2). In the left STN of ROPD patients, only the anger ERD effect was observed (450–550 ms PSO and 1950–2150 ms PSO, Table 2), and a greatly reduced broadband-gamma response to happiness was observed compared to the right STN (Table 3, happiness left vs. right STN, 400–650 ms and 1750–1900 ms PSO, $p<0.05$, $BF_{10}>3$) resulting in indistinguishable gamma responses to happy and neutral voices in the left STN ($BF_{10}<1/3$).

3.6. Effect of PD asymmetry on STN responses to emotion (Table 4)

The linear analysis of the influence of the PD asymmetry index on STN emotional responses was consistent with the results observed at the group level.

In the theta, alpha and broadband-gamma frequency bands, the strong influence of PD asymmetry on STN low-frequency responses to emotion was confirmed by a significant Condition × Asymmetry Index two-way interaction for all timings at which, at a given STN side, a vocal-emotion specific effect was observed in our main analysis (except for the left STN broadband-gamma late response [3.35–3.45 s PSO], Table 4). Interestingly, in the theta band, at the early 0.4 to 1.1 s PSO period in the left STN and at the 0.6 to 1.4 s PSO period in the right STN, while a significant influence of PD asymmetry on power was found for both angry and happy voices, this influence was significantly stronger for happiness than for anger (Table 4). A similar result was obtained for early alpha right STN emotional STN responses (0.2 to 0.6 s PSO, Table 4). Likewise, significant influences of PD asymmetry on broadband-gamma band responses to vocal emotion were observed for happy but not angry voices (Table 4). Conversely, a stronger influence of PD asymmetry on early left-STN alpha responses to angry voices was observed (0 to 0.55 s PSO, Table 4).

In the low-beta and gamma bands, in congruence with the results observed in the group analysis, linear trend analysis did not show an

Table 4
Continuous effects of the Parkinson's disease asymmetry index on power for all frequency bands in the temporal regions-of-interest (timings of significant contrasts between conditions). Time: timing of the effect. STN: left or right STN. Asymmetry and Emotion: Asymmetry: F-value and FDR corrected p-values of the main effect of the asymmetry-index OFF DOPA as well as the Emotion X Asymmetry Index two-way interaction effect on power. The remaining columns describe the z-ratio and p-value for the: ANG= trend of power with the asymmetry index for angry voices, HAP= trend of power with the asymmetry index for happy voices, NEU= trend of power with the asymmetry index for neutral voices. Contrasts reported feature the differences between asymmetry-index versus power trends for: ANG-HAP= Angry versus Happy voices, ANG-NEU= Angry versus Neutral voices, HAP-NEU= Happy versus Neutral voices.

Frequency	Time	STN	Asymmetry		Emotion: Asymmetry		ANG		HAP		NEU		ANG-HAP		ANG-NEU		HAP-NEU	
			F	p	F	p	z	p	z	p	z	p	z	p	z	p	z	p
Theta	400–1100	Left	263.48	<0.001	6.38	<0.001	6.58	<0.001	10.67	<0.001	11.28	0.000	−2.75	0.015	−3.35	0.003	−0.64	0.613
Theta	200–450	Right	198.60	<0.001	4.07	0.008	7.87	<0.001	8.37	<0.001	10.13	0.000	−0.22	0.890	−1.62	0.185	−1.42	0.249
Theta	600–1400	Right	144.81	<0.001	5.98	<0.001	4.32	<0.001	8.18	<0.001	8.99	0.000	−2.64	0.020	−3.32	0.003	−0.72	0.581
Theta	1850–2450	Right	12.78	<0.001	29.62	<0.001	−7.91	<0.001	−1.58	0.196	3.01	0.007	−4.56	0.000	−7.73	0.000	−3.27	0.003
Theta	2850–3100	Right	11.27	<0.001	5.66	<0.001	−4.21	<0.001	−2.77	0.014	0.52	0.708	−1.07	0.380	−3.34	0.003	−2.31	0.045
Alpha	0–300	Left	9.76	<0.001	29.04	<0.001	−3.61	0.001	1.93	0.106	7.05	0.000	−3.37	0.002	−2.32	0.044	1.02	0.403
Alpha	300–550	Left	3.77	<0.001	17.45	<0.001	−2.97	0.008	1.63	0.184	5.37	0.000	−6.30	<0.001	−5.43	0.000	0.81	0.532
Alpha	750–950	Left	0.41	0.008	9.99	<0.001	−2.06	0.079	−1.04	0.397	3.82	0.000	−3.19	0.004	−4.67	0.000	−1.53	0.212
Alpha	1050–1250	Left	1.44	0.233	10.18	<0.001	−1.11	0.367	1.67	0.173	4.51	0.000	−1.97	0.099	−3.99	0.000	−2.07	0.078
Alpha	2100–2600	Left	52.43	<0.001	33.64	<0.001	−9.88	<0.001	−5.45	0.000	1.41	0.249	−3.28	0.003	−8.00	0.000	−4.82	0.000
Alpha	2800–3650	Left	10.12	<0.001	36.63	<0.001	−8.75	<0.001	0.48	0.731	2.30	0.045	−6.16	<0.001	−7.83	0.000	−1.32	0.281
Alpha	200–600	Right	54.14	<0.001	26.08	0.042	−1.73	0.157	7.51	<0.001	−4.06	0.000	−6.50	<0.001	5.98	0.000	0.45	0.745
Alpha	2100–2600	Right	48.87	<0.001	23.29	<0.001	−9.93	<0.001	−1.36	0.266	−0.28	0.848	−5.68	<0.001	−6.35	0.000	−0.75	0.563
Alpha	2950–3100	Right	2.97	0.065	4.20	<0.001	−3.01	0.007	1.13	0.362	−0.87	0.492	−2.95	0.009	−1.52	0.212	1.41	0.249
Beta12	850–1000	Left	3.60	0.730	0.03	0.619	0.77	0.549	1.08	0.378	1.09	0.373	1.41	0.250	1.55	0.206	0.16	0.922
Beta12	1050–1200	Left	1.51	0.640	3.93	0.082	1.75	0.152	−1.67	0.173	1.82	0.131	2.42	0.035	−0.06	0.984	−2.47	0.030
Beta12	1500–1600	Left	10.02	<0.001	1.57	0.208	−2.49	0.029	−2.82	0.012	−0.47	0.736	1.89	0.115	1.11	0.369	−0.77	0.549
Beta12	2250–2400	Left	4.07	<0.001	4.05	0.156	−3.50	0.002	0.03	0.985	−0.03	0.985	0.22	0.890	−0.19	0.905	−0.41	0.769
Beta12	1900–2000	Right	1.22	0.063	6.30	<0.001	0.30	0.843	−3.39	0.002	1.41	0.249	2.59	0.023	−0.79	0.541	−3.39	0.002
Beta20	2100–2200	Left	40.64	<0.001	3.92	0.002	1.18	0.336	4.51	<0.001	3.46	0.002	−2.31	0.045	−1.62	0.184	0.66	0.601
L- gamma	1200–1300	Left	2.65	0.587	4.09	0.159	−1.06	0.386	2.92	0.009	1.56	0.204	−2.81	0.013	−1.86	0.123	0.93	0.456
L- gamma	200–300	Right	0.08	0.002	0.96	0.351	0.40	0.770	0.48	0.731	−1.26	0.304	−0.05	0.984	1.18	0.336	1.24	0.312
Gamma	450–550	Left	11.58	0.001	4.07	0.001	0.05	0.984	3.66	0.001	1.75	0.152	−2.53	0.027	−1.21	0.326	1.30	0.284
Gamma	1950–2150	Left	50.80	<0.001	8.93	<0.001	0.41	0.769	4.89	<0.001	4.76	0.000	−3.13	0.005	−3.09	0.006	−0.01	0.994
Gamma	2900–3200	Left	64.20	<0.001	7.77	<0.001	1.39	0.257	6.49	<0.001	4.25	0.000	−3.78	0.001	−0.73	0.576	4.51	0.000
Gamma	3350–3450	Left	16.37	0.007	3.86	0.089	−0.14	0.923	3.01	0.007	2.81	0.013	−2.21	0.057	−2.09	0.076	0.09	0.968
Gamma	200–650	Right	2.76	<0.001	12.49	<0.001	−1.31	0.284	5.66	<0.001	−0.97	0.428	−4.90	<0.001	−0.23	0.884	4.66	0.000
Gamma	700–1050	Right	47.17	<0.001	13.77	<0.001	0.19	0.905	8.57	<0.001	4.52	0.000	−5.87	<0.001	−3.07	0.006	2.76	0.014
ERP	200–300	Right	65.35	<0.001	4.48	0.243	0.68	0.594	3.05	0.007	2.34	0.043	−1.65	0.178	−1.18	0.336	0.45	0.745
ERP	400–450	Left	9.70	<0.001	0.30	0.640	−1.49	0.221	−1.58	0.196	−2.49	0.029	0.04	0.985	0.71	0.581	0.68	0.594
ERP	2750–2800	Right	0.02	0.596	0.83	0.160	−1.36	0.266	1.04	0.843	0.05	0.984	−1.70	0.165	−0.99	0.421	0.69	0.589
ERP	3250–3350	Right	6.67	0.023	3.36	0.046	1.52	0.212	−0.37	0.790	3.26	0.003	1.35	0.270	−1.24	0.312	−2.59	0.023

effect of PD asymmetry on the STN response to emotional prosody, as indicated by a non-significant Condition × Asymmetry Index two-way interaction for all timings at which, at a given STN side, a vocal-emotion effect was observed in our main analysis (except for right STN low-beta band activity at the late 1.9–2 s PSO period, Table 4).

Note that, for the ERP analysis, while a main effect of the asymmetry index was found for left and right STN early contrasts, the Condition × Asymmetry Index two-way interaction did not reach significance (Table 4).

4. Discussion

The aim of the present study was twofold. *First*, we aimed to investigate the temporal dynamics in different frequency bands of STN LFP activity during emotional prosody decoding. *Second,* we aimed to investigate the respective influence of hemispheric laterality of the STN recording site and PD side of onset on these spectral modulations. To do so, we collected intracranial recordings in the right and left STN from eight left-onset PD patients (LOPD) and six right-onset PD patients (ROPD) in response to angry, happy and neutral stimuli. After time-frequency decomposition, we conducted Bayesian and classical GLMM analyses in order to test the conjunction effects of laterality and side of onset on time-frequency correlates of emotional voice processing. We obtained a differential pattern of STN response to emotion according to the frequency band considered, with a differential susceptibility to PD asymmetry and STN hemisphere between low and high frequency activities.

4.1. Limitations of the current study

Before exploring the results of the current study in greater details, it is important to consider some limitations inherent to intracranial studies with PD patients. Because PD has been associated with modifications of the oscillatory pattern of the STN, namely an increase of beta-band activity in the sensorimotor STN (e.g. Brown and Williams, 2005; Trottenberg et al., 2007), it is unclear how the physiological activity we observed reflects the functioning of the healthy STN. However, several arguments suggest that this study reflects modulations of the STN similar to healthy physiological activity: *first*, we recorded PD patients in the ON-drug condition when they had relatively few PD signs and it is well-known that dopaminergic medication tends to normalize STN neuronal activity (Levy, 2002). *Second*, we used an experimental design where each LOPD and ROPD patient was his/her own control, so that task-related activities are unlikely to solely reflect the pathological state of PD patients. *Third*, our conservative statistical GLMM analysis included the patient as a random factor thus accounting for potential differences in patients' clinical status and differences in baseline electrophysiological pattern. As another limitation of the current study, it is important to acknowledge that, as in many clinical studies of this nature, the sample size was small (n = 14 patients included in the LFP analyses, 27 STN). That being said, our statistical analysis took into account the trial by trial variance while controlling for inter-individual differences, and used conservative outlier rejection, allowing us to be confident that the modulations we observed were not caused by a few trials but represent a global pattern of STN oscillatory activity. In addition, it should be noted that PD, and more strikingly LOPD, is associated with deficits in emotion prosody recognition that could have affected our results (J. Péron et al., 2010; Stirnimann et al., 2018). However, our paradigm focuses on implicit recognition of emotional prosody, and the differences in STN activity shown in the current study might be the substrate of differences in emotion recognition previously reported. Furthermore, a behavioral analysis performed before the LFP recordings of the current study suggested that the two patient groups were able to accurately recognize the main emotional content of the voices presented (see SI appendix).

4.2. Event-related activity: a partial replication of the previous literature

The ERP analysis performed in this study was conducted as an extension of Péron and colleagues' study (2017) but with separate LOPD and ROPD patient groups, and partially replicated its finding while providing some important new insight. Indeed, the previously observed right ERP dissociation for angry and happy voices versus neutral voices were confirmed (~220 ms and ~3000 ms PSO) in the LOPD group, while no such early dissociation was observed in the ROPD patient group, only a brief, late happy versus neutral effect in the right STN (~3000 ms PSO). As Péron and colleagues' study (2017) presented a strong majority of LOPD patients (9 LOPD/4 ROPD), we can infer that the early effects reported were driven mainly by LOPD patients. The apparent heterogeneity of evoked responses between LOPD and ROPD patients and their mixing in the earlier study may have reduced their statistical power and explain why we observed, in our LOPD group, a left STN emotional dissociation around 420 ms PSO that was absent in the previous study (Péron et al., 2017).

4.3. Three main patterns of STN oscillatory responses to emotion based on hemispheric recording site and pathological motor-symptom side of onset

We uncovered a complex pattern of oscillatory activity in terms of dependency upon PD side of onset and hemispheric laterality.

Firstly, emotional dissociations in the theta and alpha frequency bands were mostly bilaterally consistent and strongly differed according to the side of onset of the patient. The complementary linear-trend analysis confirmed that low-frequency STN responses to emotional voices covaried significantly with PD asymmetry, and that this effect of STN asymmetry differed according to the emotion of the voice presented.

In the theta band, ROPD patients presented a bilateral happiness specific ERS, which occurred later (~800 ms vs 600 ms PSO) and was shorter in duration on the left STN. A later (~2 s) anger-specific ERD then occurred in the right STN only. LOPD patients, on the other hand, presented a left-STN emotion-specific and right STN anger-specific ERS around 250–400 ms PSO. In the alpha band, ROPD patients presented a bilateral anger-specific ERD starting around 300 ms PSO. LOPD patients presented a left-STN happiness specific ERS at 750 ms PSO and a right STN anger-specific ERS at 200 ms PSO. Followed a bilateral emotion-specific ERS 1050 ms PSO in the left STN and 1400 ms PSO in the right STN.

Activity in the beta range, on the other hand, was characterized by lateralized activity which display a high level of consistency across patients' side of onset. Indeed, both LOPD and ROPD patients presented a happiness-specific low-beta ERS around 1000 ms PSO in the left STN, and our Bayesian analysis suggested for both group a slight high beta ERS for angry voices compared to happy voices around 1.5 s PSO.

In the gamma range, we observed the most striking emotional differences in the ROPD patient group. In the low gamma range, ROPD patients presented a short ERD in response to angry voices in the left STN (1200–1300 ms PSO), while LOPD patients presented an earlier short ERD for happy voices in the right STN (200–300 ms PSO). In the broadband-gamma range, LOPD patients presented only a late left STN anger-specific ERS (~3000 ms PSO), while ROPD patients presented a bilateral anger-specific response around 450 ms PSO in the left STN and 700 ms PSO in the right STN. This effect was much stronger in the right STN, however, where there was also an early happiness-specific ERS (200 ms PSO).

4.4. Influence of Parkinson's disease on STN oscillatory response to emotion

A magnetoencephalography study has shown that PD is characterized by a slowing of cortical activity, with a significant increase of theta and alpha band power and a significant decrease of beta and gamma

band power (Stoffers et al., 2007). Additionally, a reduction in whole brain EEG alpha, beta and gamma power has been described in LOPD patients compared to ROPD patients and healthy controls during perception of multimodal emotional percepts (IAPS and IADS databases, (Yuvaraj et al., 2017)). Interestingly, our results concur with these studies in two crucial ways: first, the frequency bands mainly affected by the disease side of onset were low-frequency bands (theta and alpha) previously described to present a significant power increase as a marker of PD (Stoffers et al., 2007). Furthermore, in agreement with previous observations (Yuvaraj et al., 2017), STN responses to emotion were reduced in LOPD in high frequency bands. In the low-beta band, the late happiness-specific left STN response observed in ROPD patients was abolished in LOPD patients. In the high-beta band, the only emotion-specific effect was observed in the left STN of ROPD patients and absent from LOPD patients. Finally, stronger and earlier broadband-gamma responses to emotional voices were observed in ROPD patients compared to LOPD patients.

This observation is also in coherence with deficits in emotional prosody decoding that have been shown to affect LOPD patients specifically (Stirnimann et al., 2018; Ventura et al., 2012). Furthermore, these impairments correlated with a metabolism decrease in the right OFC (Stirnimann et al., 2018) and caused a reduction in frontal ERP P200 cortical responses to emotional voices (Garrido-Vásquez et al., 2013). The reductions or delaying of LOPD patients' STN responses to emotion observed in the high frequency bands might then be a biomarker of their reduced ability to process emotional voices.

4.5. STN responses to happiness, the case for a specific deficit in Parkinson's disease

Another crucial finding of this study is that patients' side of onset mainly affected STN oscillatory responses to happiness. This result was expected as previous investigations have shown that the emotional prosody decoding impairment of LOPD patients was mainly driven by deficits in happiness recognition (Stirnimann et al., 2018). However, it is important to note that this side of onset-dependent effect takes two forms depending on the frequency bands considered.

In the strongly lateralized low-beta band, an indirect indication for an impairment of happiness-specific responses is observed in the LOPD patient group. Indeed, LOPD patients' early left STN response to happiness was delayed (1050 ms PSO in LOPD patients against 850 ms PSO in ROPD patients) and the late happiness-specific response observed in ROPD patients was absent in LOPD patients. On the other hand, linear-trend analysis of the asymmetry index in the low-frequency bands showed an effect of PD asymmetry more strongly affecting STN responses to happiness. In our group analysis, this resulted in a reduction of happiness-specific responses in the STN contralateral to the most affected side for both patient groups. Indeed, we observed in the right STN of LOPD patients a theta ERS specific to only angry voices while an overall emotion-specific response is present in the left STN. A significant reduction of alpha band activity for happiness is also observed in the right STN of LOPD patients compared to the left STN. On the other hand, we observe, in the left STN of ROPD patients, a significantly reduced happiness-specific theta ERS compared to the right STN. In the broadband-gamma band, we also observe an abolition of the early gamma happiness-specific ERS in the left STN of ROPD patients, in contrast to the right STN.

These findings seem to suggest that STN electrophysiological responses to happiness are affected in both LOPD and ROPD patients. In LOPD patients, right STN dysfunction has been shown to trigger serious impairments in happy voice prosody recognition (Stirnimann et al., 2018), suggesting a critical role of right theta and gamma and left low-beta responses to happiness for the correct decoding of this emotion. However, as no significant impairments in recognition of happy voices has been observed in ROPD patients in previous behavioral studies (Stirnimann et al., 2018), we can postulate that efficient compensatory mechanisms may be in place when left STN responses to happiness are affected. One potential mechanism underlying this resilience might involve the compensation of the impaired ROPD patients' left STN response to happiness by the early gamma response to happiness observed in the right STN of this population and not observed in LOPD patients. Similarly, the late beta response to happiness observed bilaterally in ROPD patients and absent from LOPD patients might also play a role in behavioral emotional resilience within this framework.

Another hypothesis we could formulate to explain the difference between electrophysiological and behavioral correlates of PD asymmetry, not mutually exclusive with the former, would consider the left STN as an incomplete fail-safe in the case of the dysfunction of the essential right STN for happiness decoding. Within this framework, in ROPD patients, the unaltered function of the right STN would allow preserved happiness decoding function, even in the presence of altered left STN responses to this emotion. However, in the case of LOPD patients, right STN loss-of-function might be replaced partially, albeit suboptimally, by the left STN. Indeed, it should be noted that LOPD patients still presented an above chance recognition of happiness and preserved anger recognition abilities in behavioral paradigms investigating emotional prosody decoding (Stirnimann et al., 2018). One can argue that the strong modification in low-frequency bands' pattern of responses to emotional voices observed in LOPD patients might reflect this resilience process. More specifically, we observed a strong early left STN emotion-specific theta response and a temporally overlapping happiness-specific alpha response around the same time as the happiness-specific theta response observed bilaterally in ROPD patients. These modulations might be a correlate of an incomplete left STN compensation of the impaired right STN response to happiness.

Crucially, the timing of significant electrophysiological differences between ROPD and LOPD patients in the processing of happiness also might be of importance to interpret our behavioral results (Stirnimann et al., 2018). Indeed, the current model for emotional prosody decoding postulates a processing of emotional percepts in three steps, as described in the introduction. In this regard, it is worthwhile to note that the most striking difference between the LOPD and ROPD groups we observed during the crucial second step (150–250 ms) of the emotional prosody decoding process is the right STN broadband-gamma happiness-specific ERS in ROPD patients that is completely missing in LOPD patients. We could then postulate that the impairment of this early process might impact on the processes related to the integration of acoustic parameters crucial to happiness recognition, leading to poorer accuracy in behavioral paradigms for LOPD patients.

5. Conclusion

The current investigation provided for the first time an in-depth understanding of how STN oscillatory activity is modulated by emotional voices and the influence of PD side–of-onset and hemispheric recording site on this activity. The results from the current study highlight the crucial importance of including the factor of hemispheric lateralization in future electrophysiological research in the STN of PD patients, as the effects observed, particularly in the low-frequency band, significantly varied according to the clinical characteristics of the patient's population considered. According to Péron and colleagues the STN would be involved in neural activity synchronization during the perception of an emotional stimulus (Péron et al., 2017, 2013). If this occurs in different neural networks through activity in different frequency bands, different temporal characteristics and sensitivity to PD side of onset are to be expected. The current investigation is in line with this assumption and is a strong indication that low-frequency STN activity in the emotional domain might be a biomarker of affective deficits associated with left-onset PD patients.

CRediT authorship contribution statement

Damien Benis: Methodology, Software, Validation, Formal analysis, Data curation, Writing - original draft, Visualization. **Claire Haegelen:** Conceptualization, Methodology, Investigation, Resources, Writing - review & editing, Supervision. **Philippe Voruz:** Formal analysis. **Jordan Pierce:** Writing - review & editing. **Valérie Milesi:** Software, Writing - review & editing. **Jean-François Houvenaghel:** Investigation. **Marc Vérin:** Conceptualization, Methodology, Investigation, Resources, Writing - review & editing, Supervision. **Paul Sauleau:** Conceptualization, Methodology, Investigation, Resources, Writing - review & editing, Supervision. **Didier Grandjean:** Conceptualization, Methodology, Validation, Resources, Data curation, Writing - original draft, Visualization, Supervision, Project administration, Funding acquisition. **Julie Péron:** Conceptualization, Methodology, Investigation, Validation, Resources, Data curation, Writing - original draft, Visualization, Supervision, Project administration, Funding acquisition.

Acknowledgements

We would like to thank all the included patients for their participation to this project.

Funding

The first author (DB) was funded by the Swiss National Foundation (grant no. 105314_140622 - DG and JP), and NCCR Affective Sciences was funded by the Swiss National Foundation (project no. 202 – UN7126 - DG). The funders had no role in data collection, discussion of content, preparation of the manuscript, or decision to publish.

Ethics statement

The study was approved by the ethics committee of Rennes University Hospital (approval number IDRCB: 2011-A00392–39) and all patients gave their written informed consent to participate in this study.

Data and code availability statement

Data and code are available upon request to the corresponding author.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2020.117215.

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