

Conflict-dependent dynamic of subthalamic nucleus oscillations during moral decisions

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Although lesional, neuroimaging, and brain stimulation studies have provided an insight into the neural mechanisms of judgement and decision-making, all these works focused on the cerebral cortex, without investigating the role of subcortical structures such as the basal ganglia. Besides being an effective therapeutic tool, deep brain stimulation (DBS) allows local field potential (LFP) recordings through the stimulation electrodes thus providing a physiological "window" on human subcortical structures. In this study we assessed whether subthalamic nucleus LFP oscillations are modulated by processing of moral conflictual, moral nonconflictual, and neutral statements. To do so, in 16 patients with Parkinson's disease (8 men) bilaterally implanted with subthalamic nucleus (STN) electrodes for DBS, we recorded STN LFPs 4 days after surgery during a moral decision task. During the task, recordings from the STN showed changes in LFP oscillations. Whereas the 14–30 Hz band (beta) changed during the movement executed to perform the task, the 5–13 Hz band (low-frequency) changed when subjects evaluated the content of statements. Low-frequency band power increased significantly more during conflictual than during nonconflictual or neutral sentences. We conclude that STN responds specifically to conflictual moral stimuli, and could be involved in conflictual decisions of all kinds, not only those for moral judgment. LFP oscillations provide novel direct evidence that the neural processing of conflictual decision-making spreads beyond the cortex to the basal ganglia and encompasses a specific subcortical conflict-dependent component.

Keywords: Moral decisions; Conflict; Subthalamic nucleus; Local field potentials; Deep brain stimulation.

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INTRODUCTION

Though for centuries speculation on moral behavior pertained to philosophy, recent years have witnessed an emerging scientific interest in morality and in moral cognitive neuroscience aimed at elucidating the cognitive and neural mechanisms that underlie moral behavior.

Studies investigating the neural bases of morality suggest that some moral judgments require a cognitive as well as an emotional evaluation of the conflict-generating situation (Fumagalli et al., 2009; Greene, Nystrom, Engell, Darley, & Cohen, 2004). Whereas the anterior cingulate cortex (ACC) is involved in detecting conflict, the dorsolateral prefrontal cortex (DLPFC) exerts the cognitive control to help resolve conflict. The ACC connects to the DLPFC primarily via the cortico-basal-thalamo-cortical circuit (Temel, Blokland, Steinbusch, & Visser-Vandewalle, 2005).

In a study conducted 85 years ago, Kinnear Wilson defined the basal ganglia as "the dark basement of the brain" (Wilson, 1925). Although we now know far more about their motor and cognitive functions, how these phylogenetically old structures contribute to the most sophisticated features of human behavior remains largely unknown. An insight comes from reports describing impaired decisional performance in patients with basal ganglia disorders or lesions. Patients with Parkinson's disease (PD) often have executive impairment and specific alterations in decision-making processes and in impulse control, such as pathological gambling (Smeding et al., 2006; Weintraub & Potenza, 2006).

In parkinsonian patients undergoing surgery to implant electrodes in the subthalamic nucleus (STN) for deep brain stimulation (DBS), neuronal activity can be recorded directly from the target structure. STN local field potentials (LFPs) recorded through the implanted electrodes reflect synchronized presynaptic and postsynaptic activity from large neuronal populations and can detect distributed oscillatory behaviors that are not necessarily observable in local neuronal assemblies (Brown & Williams, 2005; Foffani et al., 2003; Priori et al., 2004).

Although many studies have used LFP recordings to investigate the STN motor function (Cassidy et al., 2002; Foffani, Bianchi, Baselli, & Priori, 2005b; Kuhn, Kupsch, Schneider, & Brown, 2006b; Levy et al., 2002; Marceglia et al., 2006a, 2009; Priori et al., 2002) only few have reported STN LFP oscillations during motor imagery (Kuhn et al., 2006b) and tasks involving emotionally arousing pictures (Brucke et al., 2007; Kuhn et al., 2005), suggesting that this structure intervenes in valence-related emotional information processing. The few studies investigating the STN

role in conflict processing in various conflict tasks, such as the Stroop task (Schroeder et al., 2002), a Go/No Go task (Ballanger et al., 2009), and a visual detection task (Fleming, Thomas, & Dolan, 2010) show that the STN belongs to a complex cortico-subcortical circuit involved in conflict processing. No studies have demonstrated the STN electrophysiological role in conflictuality induced by moral judgments.

We designed this study to assess whether the basal ganglia belong to the "moral conflictual brain" and, if so, to investigate how basal ganglia circuits modulate decision-making in brain processing of conflictual stimuli. Moreover, we aimed to identify distinct oscillation rhythms for motor and cognitive information processing. To do so, in 16 patients with PD implanted with electrodes for STN DBS we investigated LFP activity in the subthalamic area in response to moral conflictual, moral nonconflictual, and neutral statements.

MATERIALS AND METHODS

Patients

We studied 16 patients with idiopathic PD (8 men and 8 women; mean $\pm$ standard deviation: age 60 ± 8.6 years, disease duration 11.8 ± 5.2 years, education 10 ± 3.2 years), all fulfilling the specific inclusion criteria for DBS treatment (Romito et al., 2002). All participants spoke native Italian. Patients' presurgery clinical status was evaluated using the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS III) before (off) and after (on) they received antiparkinsonian therapy (off therapy scores: 35.1 ± 15.3 ; on therapy scores: 14 ± 7.2). To exclude cognitive impairment, all patients underwent a complete neuropsychological evaluation. Six patients previously had behavioral disorders consequent to dopaminergic therapy. Patients' clinical details are summarized in Table 1. All patients were studied in the "on levodopa" condition, 85 ± 63.8 min after receiving their antiparkinsonian medication. None of them showed levodopa-induced dyskinesia during the experimental session. All the patients gave their written informed consent. The study was approved by the institutional review board and conformed with the Declaration of Helsinki.

All patients were bilaterally implanted in the STN with electrodes for DBS (model 3389 Medtronic, Minneapolis, MN, USA) at the neurosurgery unit of the IRCCS Istituto Ortopedico Galeazzi (11 patients) and of the IRCCS Istituto Neurologico Carlo Besta (5 patients) of Milan. The 3389 Medtronic electrode

TABLE 1
Summary of patients' clinical details (8 men, 8 women)

Patient	Age (years)	Disease duration (years)	Gender	Predominant symptoms	Behavioral disorders	UPDRS III scores On/Off drugs before surgery	Levodopa equivalent dose before surgery (mg/day)*	NMDA antagonist dose before surgery (mg/day)**	Dopamine agonist before surgery	Enzymatic inhibitor before surgery***
1	49	8	M	Freezing, dyskinesias	Pathological gambling	12/46	1400	-	-	Carbidopa, Entacapone, Rasagilin
2	60	6	F	Freezing, on-off fluctuations	Pathological gambling	12/31	940	-	Ropinirole	Carbidopa, Entacapone
3	65	10	F	Tremor, dyskinesias	-	9/25	840	-	Pramipexole	Carbidopa, Entacapone
4	67	14	F	Freezing, rigidity	-	21/34	2275	-	Pramipexole	Carbidopa
5	69	8	M	Tremor	-	23/42	1285	-	Ropinirole	Carbidopa
6	66	18	M	Freezing, dyskinesias	Pathological gambling	16/46	800	200	-	Carbidopa
7	69	14	F	Rigidity	-	7/14	745	-	Pramipexole	Carbidopa
8	63	9	F	Freezing	-	10/27	257.5	200	Pramipexole	Carbidopa, Entacapone
9	61	25	M	Tremor, motor fluctuations, dyskinesias	-	28/63	1232.5	200	Ropinirole	Carbidopa, Entacapone
10	59	6	F	Motor fluctuation	Punding	6/16	1282.5	200	Pramipexole	Carbidopa, Entacapone
11	63	19	M	Rigidity	-	25/58	1185	-	Ropinirole	Carbidopa
12	41	15	M	On-off fluctuations, hyperkinesias	Pathological gambling	9/34	550	-	-	Carbidopa, Entacapone
13	64	11	F	Motor fluctuations, hyperkinesias	-	10/26	910	-	Pramipexole	Carbidopa, Entacapone
14	58	8	M	Motor fluctuations, rigidity, parenthesis	Hypersexuality	17/50	1535	-	Pramipexole	Carbidopa, Entacapone
15	64	9	M	Motor fluctuations, rigidity, parenthesis	-	6/15	1280	-	Pramipexole	Carbidopa, Entacapone
16	42	10	F	Rigidity, dyskinesias	-	12/48	730	-	Ropinirole	-

*Preoperative levodopa equivalent dose expressed in mg/day represented the sum of levodopa and dopamine agonist. Dopamine agonist equivalent doses were calculated with the following equivalences: 100 mg levodopa = 2 mg apomorphine = 1 mg pergolide = 1.5-2 mg cabergoline = 1 mg pramipexole = 10 mg bromocriptine = 5 mg ropinirole (LIMPE, 2002). **N-methyl-D-aspartate antagonists (NMDA) dose is the amantadine dose (mg/day). ***Inhibitor of enzyme involved in degrading levodopa (enzymatic inhibitor): catechol-O-methyl transferase inhibitor (COMT); monoamine oxidase inhibitor (MAOI); dopa decarboxylase inhibitor (DDCI).

implanted has four cylindrical contacts (1.27 mm in diameter, 1.5 mm in length, placed 2 mm apart, center-to-center) denominated 0-1-2-3, beginning from the more caudal contact. In all nuclei studied, contact 1 was placed within the optimal functional target assessed through electrophysiological monitoring procedures, including recordings to evaluate the neuronal signal along the trajectories and assessment of DBS-induced changes in rigidity in various electrode locations. The optimal functional target was defined as the position at which DBS induced maximal changes in rigidity with a good therapeutic window (threshold for side effects $> 1.5 \times$ threshold for clinical effect). DBS electrodes' location was confirmed in all patients by immediate postoperative stereotactic magnetic resonance imaging (MRI) (Table 2).

The surgical procedure used in the two hospitals has been detailed elsewhere (Marceglia et al., 2010): for IRCCS Istituto Ortopedico Galeazzi by Rosa et al. (2010) and for IRCCS Istituto Neurologico Carlo Besta by Franzini, Ferroli, Leone, Bussone, and Broggi (2004).

Moral task

The moral task was constructed on the basis of the visual sentence verification task used by Moll, de Oliveira-Souza, Bramati, and Grafman (2002a). The task consisted of 38 sentences divided into 13 neutral, 10 moral conflictual, and 15 moral nonconflictual statements. Each statement was presented in a random order for a maximum of 10 s. During this period, participants were instructed to read each sentence and to respond if they agreed or disagreed with it by pressing the "A" (agreement) or the "L" (disagreement) keys with the left or the right finger. After the key was pressed, a black screen was displayed for 1 s before the next statement appeared on the screen. Subjects were instructed to respond as quickly and accurately as possible. Stimuli were presented in Italian on a PC screen using Presentation Software (Neurobehavioral Systems, Albany, CA). Reaction times (RTs) were stored for further analysis.

Examples of neutral items are *A piano has black and white keys* and *Sleep is an essential component of life*. Examples of moral conflictual items include *Stealing is right when it is useful to save a human life* and *Some crimes must be punished by the death sentence*. Examples of moral nonconflictual items are *All men have the right to live* and *Child labor is forbidden* (Figure 1A).

Sentences presented to patients were selected from a larger database consisting of 192 sentences with

cultural or socio-moral content. Sentences were comparable for number of words, length of words, familiarity and frequency of use. Statements were administered to 44 healthy subjects (17 men, 27 women, age 47.6 ± 12.3 years; education 12.1 ± 3.9 years). Each sentence was evaluated on a five-point Likert scale (ranging from 1 = "not at all" to 5 = "very much") about "understandability" (How hard was

TABLE 2
Target coordinates for the 16 patients

Patient	Recorded side	Target coordinates (mm)		
		X	Y	Z
1	Right	12.0	4.0	4.0
	Left	12.0	4.0	4.0
2	Right	11.6	3.0	1.5
	Left	10.3	4.1	1.6
3	Right	12.9	0.5	2.3
4	Right	12.0	4.0	4.0
	Left	12.0	4.0	4.0
5	Right	11.7	2.0	1.4
	Left	13.0	2.2	1.6
6	Right	12.0	4.0	4.0
	Left	12.0	4.0	4.0
7	Right	11.6	0.8	1.4
8	Right	12.6	3.8	1.0
9	Left	12.3	3.0	1.9
10	Right	11.8	3.0	2.4
	Left	12.3	2.3	1.8
11	Right	11.2	2.3	2.1
	Left	12.0	3.1	2.0
12	Right	12.0	5.0	4.0
	Left	12.0	5.0	4.0
13	Right	10.7	1.2	2.6
	Left	11.3	3.1	2.1
14	Right	12.3	2.1	1.9
	Left	11.8	2.5	2.3
15	Right	11.3	2.4	3.0
	Left	11.7	2.1	1.6
16	Right	12.0	5.0	4.0
	Left	12.0	5.0	4.0

Coordinates were accorded to anterior commissural-posterior commissural (AC-PC) line and midcommissural point (MCP); X = lateral from midline; Y = posterior from MCP; Z = ventral to AC-PC line.

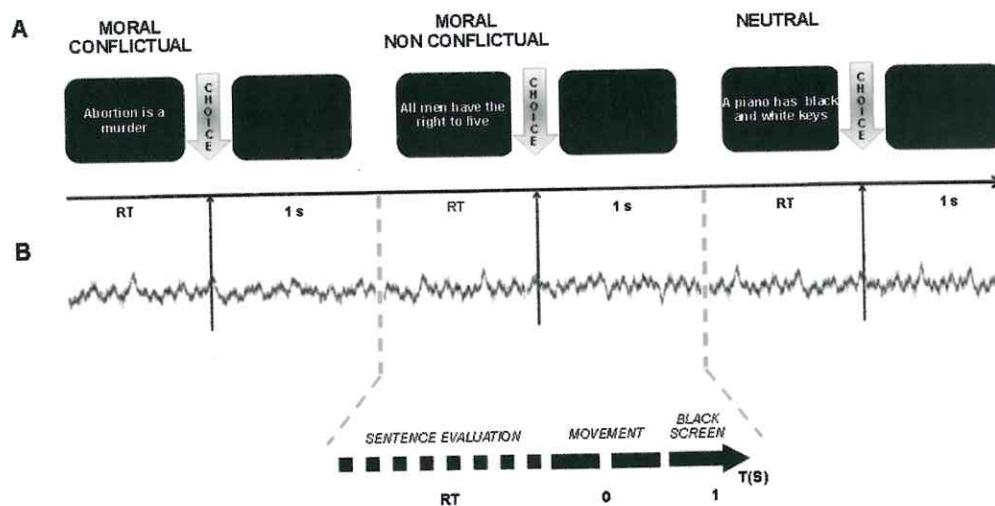


Figure 1. Moral task. (A) Timeline for the experimental protocol and three examples of moral conflictual, moral nonconflictual, and neutral statements. During the moral task, participants read the sentence on the PC screen: if they agreed with the statement they pressed the “A” key with the left finger and if they disagreed with it they pressed the “L” key with the right finger. After subjects pressed the key, a black screen was displayed (1 s) before the next statement appeared on the screen. (B) An example of the raw signal for the subthalamic nucleus local field potentials (STN LFPs). Dashed lines divide the signal in trials and the arrows represent key pressing (trigger). Each trial comprised three phases: sentence evaluation, movement, and black screen.

sentence understanding?), “moral content” (Has the sentence a moral value?), “conflictuality” (Do you think the sentence is morally conflictual?) and “emotional value” (Did you have an emotional reaction to the sentence?). Subjects also expressed their agreement or disagreement with the content of the sentence.

As a first step, we selected items that achieved a mean score of <2 on the “understandability” scale, namely the most understandable sentences. Then, we defined as “moral” sentences all the items evaluated by all subjects on the “moral content” scale with a score of >3.5 and balanced for the “emotional value” scale. These sentences were classified as conflictual and nonconflictual. Conflictual sentences included all items evaluated by all subjects on the “conflictuality” scale with a score of >3 , whereas nonconflictual items included all sentences evaluated by all subjects on the “conflictuality” scale with a score between 2 and 3, where 2 was the lowest value given for moral sentences. Neutral sentences were selected from statements evaluated with the moral content scale, conflictuality scale, and emotional value scale with a mean score of <1 . Sentences were balanced for length and number of words. To ensure a balanced number of sentences eliciting an expected response with the left or the right key, selected items were also balanced for the expected response (“I agree” or “I disagree”) on the basis of participants’ responses. Conflictual sentences had a mean value of 3.8 on the “moral content” scale and 3.3 on the “conflictuality” scale. Nonconflictual

sentences had a mean value of 3.7 on the “moral content” scale and 2.3 on the “conflictuality” scale.

Cognitive and psychological assessment

Before performing the moral task, patients underwent a short cognitive and psychological assessment using the Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) for a global cognitive evaluation and three 100 mm visual analog scales (VAS): a mood VAS (0 corresponding to good mood and 100 corresponding to bad mood), a happiness VAS (0 corresponding to happiness and 100 corresponding to sadness), and an anxiety VAS (0 corresponding to anxiety and 100 corresponding to absence of anxiety). Patients were asked to describe their current emotional state by marking each line (Aitken, 1969).

Electrophysiological assessment

During the moral task, LFPs were recorded from the implanted DBS electrodes 4 days after surgery, before the electrodes were connected to subcutaneous high-frequency stimulator. For LFP recordings, subjects were comfortably seated in an armchair. LFPs were bipolarly captured from the 3389 electrodes using the closely spaced pair of contacts 1–2, corresponding to the optimal functional target and its nearest dorsal contact.

Signals were preamplified, filtered (band pass 2–512 Hz), differentially amplified (100,000 $\times$) and digitized with 1024 Hz sampling rate and 12 bit quantization with 5 V range through the Galileo BE Light EEG amplification system (EBNeuro Spa, Florence, Italy). All data were analyzed offline with Matlab software (version 7.3, The MathWorks, Natick, MA).

To highlight frequency components in the classic EEG range, signals were band-passed 2–45 Hz with a Finite Impulse Response (FIR) filter. LFPs were first analyzed in the time–frequency domain through a non-parametric approach based on the Fourier transform (FT).

In the frequency domain oscillations were quantified through their power spectral density (PSD), estimated using the multitaper method (Percival & Walden, 1993), a technique that applies Thomson's adaptive nonlinear combination of modified periodograms (Thomson, 1982). Periodograms were computed using a sequence of orthogonal tapers (i.e., windows in the frequency domain) specified from the discrete prolate spheroidal sequences. The first PSD analysis was designed to evaluate changes in the oscillatory pattern during each trial, comprising the presentation, evaluation, answer to a single sentence (corresponding to the RT), and the ensuing black screen (1 s). The signal corresponding to a single trial was defined starting from presentation of the sentence, moving forward for a number of samples corresponding to the mean RT value for each task condition (moral conflictual, moral nonconflictual, and neutral, see Results, Behavioral data) and adding a further 1 s after the answer corresponding to the black screen. In each trial, a time-moving Hanning window, 500 ms long, was applied to the signal; the window was moved forward 250 ms obtaining a segment 500 ms long every 250 ms advance and each segment overlapped the previous by 250 ms. The PSD was calculated for each 500 ms segment then averaged across trials to obtain the mean power spectrum for each 500 ms segment. To account for interindividual variability, the average PSD was normalized by the total spectral power (integral of the PSD in the 2–45 Hz) calculated while subjects observed the black screen after a neutral sentence.

The resulting time–frequency spectrum was obtained considering the sequence of the normalized average PSD in each 500 ms segment, with a final time resolution of 250 ms and a frequency resolution of 2 Hz.

Because each RT comprised reading, sentence evaluation, and subject's movement to press the key (trigger) and respond, each trial comprised three phases: "sentence evaluation", "movement", and "black screen"

(Figure 1B). The estimated length of each phase was derived from the time–frequency analysis (see Results).

To analyze LFPs in each phase, the power spectrum was estimated with a "static" approach, considering the entire phase as a stationary process that entailed no modulations within the phase, and modulations only between different phases. Instead of a time–frequency analysis we therefore used a static power spectral analysis. Static PSDs were calculated in each phase in each trial with a frequency resolution of 1 Hz, then averaged across trials dividing moral conflictual, moral nonconflictual, and neutral task conditions and normalized by the total spectral power while subjects observed the black screen after the neutral condition. The analysis focused on two main oscillations, the 5–13 Hz and 14–30 Hz bands, hereafter defined as low-frequency and beta bands. Frequency bands were analyzed estimating the spectral power, calculated as:

$$SP_B = \sum_{f \in B} PSD(f)$$

where B is the band of interest (5–13 Hz; 14–30 Hz) and SP is the spectral power.

To elucidate the time course of single band during the decision-making process, the Hilbert transform was used to determine the instantaneous, so-called analytic amplitude and phase of a given bandpass signal (McDonough & Whalen, 1995). To apply the Hilbert transform, the signal was band-passed in the band of interest and squared to obtain signal power. Because the frequency resolution was limited to a single band, the Hilbert transform achieved an extremely high temporal resolution (0.97 ms). The first step in computing the analytic signal for a given frequency band was to treat the original signal with a corresponding bandpass filter. To obtain the Hilbert transformed signal, the band-passed spectrum was multiplied in the frequency domain by the imaginary signum function, and the inverse Fourier transform was then applied, yielding the analytic signal. The squared modulus of the Hilbert transform averaged across trials corresponding to the same sentence type (moral conflictual, moral nonconflictual, and neutral) was considered to describe event-related modulations (power modulations).

Because trial RTs for each patient differed in the three task conditions, to compare the timing of power modulations within the sentence evaluations in each task condition we decided to define a percentage time. The percentage time stretches or contracts the sentence evaluation phase to the mean value of moral conflictual, moral nonconflictual, and neutral task condition RTs using the cubic spline interpolant (de Boor, 1978). We

also analyzed 1 s of black screen before and after the new signal without altering real time. This procedure produced a time that started at 0 (first sample of the black screen in the preceding trial) and ended at 100% (last sample of the black screen following the answer). Power modulations were averaged across trials of the same task condition and were defined as percentage power changes in the mean value of both black screens.

Statistical analysis

Task conditions RTs were tested with a one-way repeated measures analysis of variance (ANOVA) with "moral conflictual", "moral nonconflictual", and "neutral" levels. To evaluate the role of gender, we applied a two-way mixed-model ANOVA with sentence type as within-factor (moral conflictual, moral nonconflictual, and neutral) and gender as between-factor (man and woman). The role of education was investigated using a two-way mixed-model ANOVA with sentence type as within-factor (moral conflictual, moral nonconflictual, and neutral) and education as between-factor (5, 8, or 13 years). Moreover, we assessed whether mood, happiness, anxiety and global cognitive state were correlated with RTs. To do so, Pearson's linear correlation coefficient was calculated between mood VAS, happiness VAS, anxiety VAS, and moral conflictual, moral nonconflictual, and neutral RTs, and between MMSE and RTs. To evaluate whether behavioral disorders influenced patients' performance, we applied a two-way mixed-model ANOVA with sentence type as within-factor (moral conflictual, moral nonconflictual, and neutral) and behavioral disorders as between-factor (presence and absence).

Because the statistical analysis considered the two frequency bands (low-frequency and beta) as independent variables, each statistical test was applied to each frequency band. In a preliminary analysis, to verify whether LFPs change during the three phases of the decision-making process in the three task conditions, considering the presence or absence of behavioral disorders as well, we used a three-way mixed-model ANOVA. The first within-factor was task condition (moral conflictual, moral nonconflictual, and neutral), the second within-factor was phase (sentence evaluation, movement, and black screen) and the between-factor was behavioral disorders (presence and absence).

Power modulations were studied in the frequency band of interest. Changes were assessed by two-way repeated measures ANOVA with the first factor task condition (moral conflictual, moral nonconflictual, and neutral) and the second factor phase (black screen and

sentence evaluation). The Tukey honest significant difference test was used for post-hoc analyses. Differences were considered significant at $p < .05$.

RESULTS

Behavioral data

One-way ANOVA with moral conflictual, moral nonconflictual, and neutral RTs as within-factors revealed a significant difference between the three conditions, $F(2, 30) = 18.7$; $p < .0001$; moral conflictual: 6316.8 ± 752.3 ms; moral nonconflictual: 5339.1 ± 965.6 ms; neutral: 6067.7 ± 1122.0 ms. Post-hoc showed that despite no differences in RTs between moral conflictual and neutral ($p = .450$) and moral nonconflictual and neutral conditions ($p = .064$), RTs to moral conflictual sentences were significantly higher than RTs to moral nonconflictual sentences ($p = .005$).

Neither gender nor education influenced RTs ($p > .05$ in all cases). Mood and happiness VAS were significantly inversely correlated with moral nonconflictual RTs, $r^2 = .389$, $p = .0299$ and $r^2 = .426$, $p = .0212$. No correlation was found between anxiety VAS and RTs, or between MMSE and RTs. The presence of behavioral disorders did not significantly influence RTs, $F(2, 28) = 2.16$, $p = .1347$.

Electrophysiological data

Time-frequency plots of the LFP spectrum averaged across all patients using the mean value of task condition RTs in all trials in all patients (6316.8 ms for moral conflictual, 5339.1 ms for moral nonconflictual, and 6067.7 ms for neutral) and 1 s after the answer (black screen) showed that the predominant oscillation concentrated in the low-frequency band (5–13 Hz) (Figure 2). Although power in the low-frequency band changed during each task condition, it increased more prominently during conflictual than during nonconflictual and neutral task conditions. Conversely, beta band (14–30 Hz) power changed in all task conditions but increased mainly during movement execution.

We therefore defined the movement phase as starting from 500 ms before to 500 ms after key pressing (Foffani et al., 2005b; Kuhn et al., 2006a; Levy et al., 2002) and the sentence evaluation phase as starting from sentence presentation to 500 ms before key pressing. Hence, each STN LFP trial comprised three previously defined phases. When we estimated the PSD for each phase we found that spectral power concentrated in the low-frequency band, displaying a broad peak in

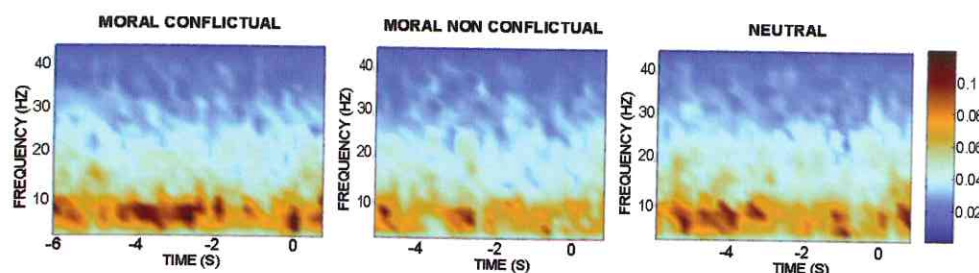


Figure 2. Time–frequency plots of grand average subthalamic nucleus local field potentials (STN LFPs) in each task condition: moral conflictual, moral nonconflictual, and neutral conditions. The x-axis shows the time (s) from the mean reaction time value of the task condition (moral conflictual: 6316.8 ms; moral nonconflictual: 5339.1 ms; neutral: 6067.7 ms) to 1 s after the choice; TIME = 0 s corresponds to the value sampled when the subject pressed the key (trigger). The y-axis is frequency (Hz). Red represents power increase and blue power decrease. Power was normalized by the total average spectral power of the black screen displayed after neutral condition (the first second after the trigger) in arbitrary units (AU). Note that, during the moral task, whereas beta power changed only during the movement phase, low-frequency power increased during all task conditions, specifically in moral conflictual sentences.

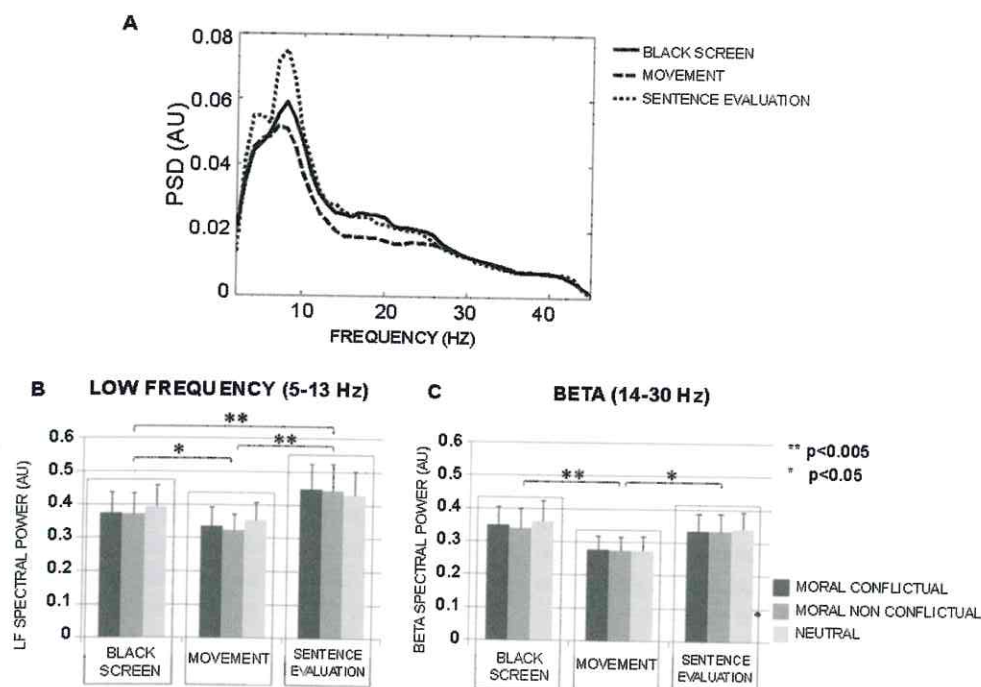


Figure 3. Spectral analysis during black screen observation, movement, and sentence evaluation. (A) Power spectral density (PSD) of subthalamic nucleus local field potentials (STN LFPs) grand average ($n = 16$) during the three phases: black screen (1 s after the key was pressed), movement (from 500 ms before to 500 ms after the key was pressed), and sentence evaluation (from sentence presentation to 500 ms before the key was pressed); each PSD was normalized by the total spectral power of the PSD in the 2–45 Hz frequency band in the black screen phase after the neutral condition. x-axis: frequency (Hz, linear scale); y-axis: PSD (arbitrary units, AU, linear scale). (B) Histograms represent the low-frequency band power (5–13 Hz) in the three phases during each task condition. Error bars represent the confidence interval of the estimated mean ($1.96 \times$ standard error). $*p < .05$, $**p < .005$, three-way mixed-model ANOVA. x-axis: three phases (black screen, movement, and sentence evaluation) in each task condition (moral conflictual, moral nonconflictual, and neutral); y-axis: normalized spectral power in arbitrary units (AU). (C) Histograms represent the beta band power (14–30 Hz). Note that whereas low-frequency oscillations changed only during sentence evaluation and movement, beta oscillations changed only during movement.

the 5–13 Hz and very low activity in the beta band (14–30 Hz) (Figure 3A). The low-frequency oscillation, whatever the task condition and the presence of behavioral disorders, was significantly higher while the patient made the decision, factor phase, $F(2, 52)$

$= 23.34$, $p < .0001$, factor task condition, $F(2, 52) = 0.67$, $p > .05$, factor behavioral disorder, $F(1, 26) = 1.84$, $p > .05$, no significant interactions, than while they observed the black screen, post-hoc, sentence evaluation vs. black screen, $p = .0009$, or moved to make the

TABLE 3
Spectral power values during the moral task

		LF (5–13 Hz) (AU)		BETA (14–30 Hz) (AU)	
		Mean interval	Confidence interval	Mean	Confidence interval
Black screen	Moral conflictual	0.3744	0.0625	0.3484	0.0574
	Moral nonconflictual	0.3728	0.0601	0.3408	0.0582
	Neutral	0.3922	0.0663	0.3617	0.0622
Movement	Moral conflictual	0.3355	0.0576	0.2761	0.0411
	Moral nonconflictual	0.3237	0.0468	0.2748	0.0414
	Neutral	0.3541	0.0532	0.2758	0.0412
Sentence evaluation	Moral conflictual	0.4475	0.0785	0.3361	0.0508
	Moral nonconflictual	0.4444	0.0803	0.3359	0.0525
	Neutral	0.4311	0.0715	0.3418	0.0522

Normalized spectral power expressed in arbitrary units (AU) in the low-frequency band (LF, 5–13 Hz) and beta band (BETA, 14–30 Hz) in the three phases during each task condition (mean and confidence interval).

decision pressing the computer key, post-hoc, sentence evaluation vs. movement, $p = .0001$ (Figure 3B; Table 3). Conversely, power in the beta band, independently from the task condition and the presence of behavioral disorders, changed only during movement, factor phase, $F(2, 52) = 10.63$, $p < .0001$, factor task condition, $F(2, 52) = 1.97$, $p > .05$, factor behavioral disorder, $F(1, 26) = 0.00$, $p > .05$, no significant interactions; post-hoc, sentence evaluation vs. movement, $p = .0021$; black screen vs. movement, $p = .0002$ (Figure 3C; Table 3). The low-frequency band therefore changed during decision-making and the beta band during movement. Power patterns in neither frequency band were influenced by the previous presence of behavioral disorders, mean $\pm$ standard deviation, arbitrary unit; presence 0.4297 ± 0.1766 vs. absence 0.3387 ± 0.1721 , $F(1, 26) = 1.84$, $p > .05$.

When we applied the Hilbert transform to highlight differences in the low-frequency band between task conditions that an analysis considering the sentence evaluation phase as a whole static process might underestimate, and to focus on a single band, thus yielding the maximal time resolution, we found that low-frequency power modulation was significantly higher during the moral conflictual condition than in the other conditions (Figure 4). ANOVA disclosed that low frequencies increased significantly more during sentence evaluation than during black screen, factor phase, $F(1, 27) = 74.01$, $p < .0001$, and that they differed between task conditions, $F(2, 54) = 3.73$, $p = .0305$. It also showed a significant interaction between the two factors, task condition $\times$ phase, $F(2, 54) = 3.73$, $p = .0304$: low-frequency power modulation was significantly higher during the moral conflictual condition than during the moral nonconflictual, post-hoc test, mean $\pm$ confidence interval,

%: 37.3 ± 13.1 vs. 26.6 ± 6 , $p = .0477$, and neutral condition, 37.3 ± 13.1 vs. 23.3 ± 7.6 , $p = .0083$.

No significant difference was found between the moral nonconflictual and neutral conditions ($p > .05$).

DISCUSSION

By recording STN oscillations in patients with PD during the execution of a moral task, we investigated the role of basal ganglia in moral decision-making and in the processing of conflictual stimuli. Our results showed that whereas the beta oscillations are prevalently involved in motor functions, the low-frequency subthalamic rhythms are specifically, and in a conflict-dependent way, involved in decision processing. We provide the neurophysiological evidence that the STN intervenes in moral judgment and conflictuality processing, therefore advancing current knowledge on the basal ganglia role in human decision-making processes.

The LFP oscillations we recorded from the implanted electrodes differed during the three phases in the moral task, highlighting different motor and cognitive information processing. Whereas low-frequency power increased significantly more during sentence evaluation than during movement phase and black screen, beta band oscillations differed only during movement; specifically, beta oscillations decreased more in the movement phase than in the other conditions. This specific modulation suggests that STN processing during sentence content evaluation specifically involves changes in the low-frequency band. Conversely, STN processing during movement execution involves changes in the beta band, confirming previous observations (Alegre et al., 2005; Cassidy et al., 2002; Foffani et al.,

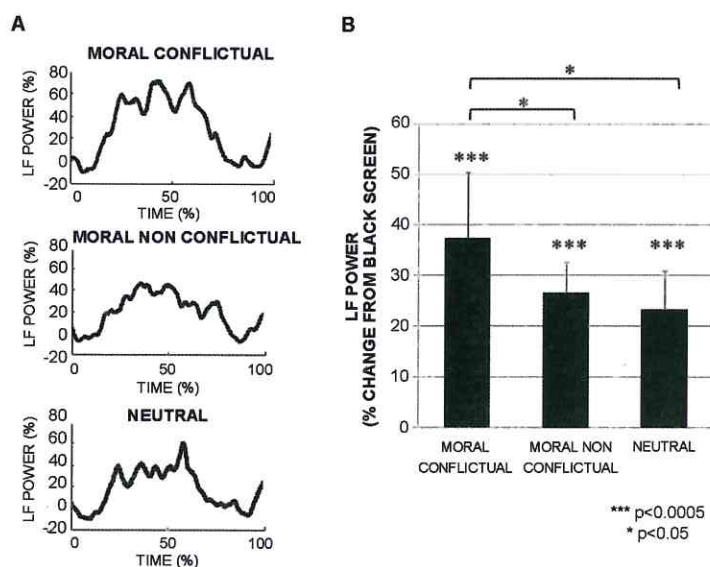


Figure 4. Low-frequency power modulation during the sentence evaluation for moral conflictual, moral nonconflictual, and neutral statements. (A) Grand average ($n = 16$) of the low-frequency (LF) power modulations for each task condition (moral conflictual, moral nonconflictual, and neutral), expressed as percentage change from the black screen phases. LF power modulations were estimated from 1 s before the sentence was displayed to 1 s before the next statement appeared on the screen; the interval between the two black screens represents sentence evaluation. x-axis: time (%; see Methods); y-axis: LF Hilbert-power modulations (%). (B) Histograms represent the mean LF Hilbert modulation in sentence evaluation during each task condition. Error bars represent the confidence interval of the estimated mean ($1.96 \times$ standard error). $*p < .05$, $***p < .0005$, two-way ANOVA. x-axis: three task conditions (moral conflictual, moral non-conflictual, and neutral); y-axis: LF power modulation (%). During sentence evaluation, mean LF power increased significantly from values during black screen in each task condition (moral conflictual, $p = .0001$; moral nonconflictual, $p = .0001$; neutral, $p = .0001$). Note the significantly higher LFP power modulation during the moral conflictual condition than during the other two conditions (moral conflictual vs. moral nonconflictual, $p = .0476$; moral conflictual vs. neutral, $p = .0083$).

2005b; Kuhn et al., 2004; Priori et al., 2002). Our findings suggest that LFP rhythms are independent channels dedicated to different forms of information processing. Previous literature showed low-frequency LFP modulations after drug administration, during and after STN stimulation, and found that the changes correlated with parkinsonian patients' clinical features. Specifically, in the "on" state after levodopa and apomorphine intake low-frequency activity increased, showing dopamine-dependent LFP changes, whereas non-dopaminergic drug intake left LFP activity unchanged (Marceglia et al., 2006b; Priori et al., 2004). Also, an abnormal increase in low-frequency activity correlated with dyskinesia (Alonso-Frech et al., 2006; Foffani et al., 2005a). STN low-frequency oscillations increased during ongoing STN DBS (Rossi et al., 2008), confirming previous observations reporting that the 1–1.5 Hz band power increased and slowly decayed to baseline levels after DBS was turned off (Priori et al., 2006). Because we studied all our patients while they were on therapy and off stimulation without dyskinesia, we excluded possible medication and DBS-induced changes in low-frequency modulation.

Among the few previous studies investigating the role of the STN in cognitive functioning, Wahl et al.

(2008) first investigated the role of the STN, thalamus, and globus pallidus internus in processing syntactic and semantic features of auditorily presented language. These data suggested that the thalamus, but not the basal ganglia, is involved in syntactic and semantic language processing. Two studies, Kuhn et al. (2005) and Brucke et al. (2007), investigated STN involvement in emotional processing and found that 8–12 Hz LFP activity was modulated by pleasant and unpleasant emotional stimuli, showing affective activation in the STN. These studies demonstrated that the low-frequency band is an important channel for encoding various stimuli, including cognitive and emotional information.

When we investigated whether STN processing differed between types of statement, we found that low-frequency power increased significantly more during conflictual than during nonconflictual and neutral conditions. This difference implies that low-frequency STN LFP activity intervenes specifically during conflictuality. We therefore suggest that STN is influenced neither by the pure cognitive evaluation of neutral sentences based on cultural and encyclopedic knowledge, nor by the "morality" feature, or moral content of the sentences presented. If this had been so, the STN would

have responded to conflictual and nonconflictual moral sentences. Alternatively, in line with Kuhn et al. (2005) and Brucke et al. (2007), the LFP oscillations we recorded during the moral task might reflect a response to emotionally salient sentences. This explanation seems unlikely, however, given that STN activity remained unchanged during the moral nonconflictual items compared with the moral conflictual ones, both of which were equally balanced on the emotional value scale. We therefore conclude that low-frequency STN oscillations have a pivotal role in conflict processing.

Evidence that STN has a role also in cognitive and emotional processes fits in well with its known anatomical connections. The STN belongs to the cortico-basal-thalamo-cortical network, which tightly connects the basal ganglia to the cortex, specifically to the DLPFC and orbitofrontal cortex for the "associative" circuit, to the limbic and paralimbic cortices, hippocampus, and amygdala for the "limbic" circuit, and to the primary motor, premotor, and somatosensory cortices for the "motor" circuit. These manifold connections define the STN as a nexus for integrating the motor, cognitive and emotional components of behavior (Mallet et al., 2007). The associative and limbic circuits involve the same cortical areas related to moral and conflict processing. Particularly, the DLPFC is related to the deployment of cognitive control in responding to information with moral content (Greene et al., 2004) and to conflictual stimuli (Miller & Cohen, 2001), the orbitofrontal cortex is associated with alterations in decision-making and moral processing (Ciaramelli, Muccioli, Ladavas, & di Pellegrino, 2007; Fumagalli et al., 2010; Koenigs et al., 2007; Moretto, Ladavas, Mattioli, & di Pellegrino, 2010) and is related to response inhibition and impulsivity control (Fleming et al., 2010) and the ACC is involved in detecting conflict during reasoning on moral dilemmas (Greene et al., 2004), and according to Botvinick, serves to monitor conflicts in information processing, to monitor action outcomes and to guide decision-making (Botvinick, 2007; Botvinick, Cohen, & Carter, 2004; Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999).

Whereas no study has specifically examined moral judgment in PD, some studies investigated economic decision-making. For example, Frank, Samanta, Moustafa, & Sherman (2007) investigated reaction times during a probabilistic selection task focused on the decision between high and low conflictual options in patients with PD on and off STN DBS, and on and off dopaminergic medication. They found that STN DBS selectively interferes with the normal ability to slow down when facing decision conflict. When studied while

on DBS, patients speeded up their decisions under high-conflict conditions. This study provided behavioral evidence that the STN intervenes in processing conflictual stimuli. In their study, Frank et al. (2007) defined conflict as the necessity to decide between two items, both leading to a win or a loss. From the results obtained, they elaborated a neurocomputational model of basal ganglia functioning during economic decision-making. According to this model, the different STN responses to decisional conflict are mediated by the presupplementary motor area and the cingulate cortex, brain regions involved in detecting and integrating response conflict. This hypothesis is also supported by a study by Ballanger et al. (2009), who confirmed STN involvement in high-conflict decisions. Specifically, they showed that STN stimulation impaired the ability of patients with PD to slow down their responses to high-conflict decisions. Measuring regional cerebral blood flow, they also found that STN stimulation is associated with reduced activation in the left premotor cortex, presupplementary motor area, dorsal ACC, and inferior frontal cortex. All these structures involved in detecting and integrating response conflict (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Botvinick et al., 1999, 2004; Buchsbaum, Greer, Chang, & Berman, 2005; Simmonds, Pekar, & Mostofsky, 2008). Another relevant study about the neural bases for difficult decisions (Fleming et al., 2010) found that the STN specifically contributed to decide about high-difficult vs. low-difficult choices. High-difficult choices induce in the subjects a conflictual state that seems strictly to involve the STN, owing to its connections to medial and inferior frontal cortices. A neuroimaging study showed that conflict moral decisions were associated with increased activity in the ACC and DLPFC, the ACC having a role in conflict detection, and the DLPFC in cognitive control (Greene et al., 2004). We believe that this anatomic explanation of conflictuality holds true for decisions of all kinds, including moral judgment. Another relevant account of moral processing emerges from the hypothesis about the integration of content- and context-dependent information, motivations, social features and moral emotions (Moll & De Oliveira-Souza, 2007; Moll et al., 2002b; Moll, Zahn, de Oliveira-Souza, Krueger, & Grafman, 2005). According to this hypothesis, the conflictual sentences, concerning for example abortion, murder, and capital punishment, elicited a differential response in STN activity due to their content, which reflects a behavior that deviates from moral and social values and from norms. In line with this theory, the STN is a structure involved in the functional integration among moral values, norms, moral emotions,

motivations, and the execution of goal-oriented behaviors. Whereas the conflictual account considers STN as a key structure in the emotional and cognitive processing of conflictual stimuli, the integrative theory would explain the STN conflictual-related activity as the result of distortions of moral values or moral emotions, emerging from the integration between the STN and the cortical and limbic areas functions.

Further support for STN involvement in emotional and cognitive processing comes from the clinical features of PD. The ability to face up to conflictual decision pertains to various executive functions, such as problem-solving, planning and regulating behavior, and inhibition, all commonly impaired in patients with advanced PD (Koerts, Leenders, & Brouwer, 2009). PD frequently leads also to behavioral alterations, specifically to impulse control disorders, such as compulsive gambling and sexual behavior. These behavioral disorders often manifest during dopamine replacement therapy (Weintraub & Potenza, 2006).

A potential limitation of this study is that because individual subjects' moral behavior was irrelevant to our physiological question, we did not evaluate moral behavior in our patients by interview or questionnaire. Because inadequate moral judgment is a typical feature in patients with behavioral and cognitive alterations due to prefrontal lesions (Koenigs et al., 2007), and because these patients were excluded by DBS inclusion criteria, we consider it unlikely that our patients were morally inadequate.

In conclusion, we observed LFP modulations throughout a moral decision-making task, highlighting the dynamic involvement of specific STN oscillations in the emotional and cognitive processing of conflictual stimuli in patients with PD. Our findings therefore extend the "moral conflictual brain" to encompass the basal ganglia including the STN, especially for conflict processing. An intriguing topic for future research might be to clarify the neural processing of moral conflictual decision-making by studying medication- and DBS-induced changes in low-frequency LFP oscillations during the moral task.

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