RESEARCH ARTICLE

Different effects of levodopa and subthalamic stimulation on emotional conflict in Parkinson's disease

Raul Martínez-Fernández^{1,2,3} | Astrid Kibleur³ | Stéphan Chabardès^{3,4} |
Valérie Fraix^{2,3} | Anna Castrioto^{2,3} | Eugénie Lhommée^{2,3} | Elena Moro^{2,3} |
Lucas Lescoules³ | Pierre Pelissier^{2,3} | Olivier David³ | Paul Krack^{2,3,4,5}

¹CINAC-Hospital Universitario HM Puerta del Sur, Móstoles, Universidad CEU San Pablo, Madrid, Spain

²Movement Disorders Unit, CHU Grenoble Alpes, Grenoble, France

³U1216, Grenoble Institut des Neurosciences, Inserm, Université Grenoble Alpes, Grenoble, France

⁴Neurosurgery Department, CHU Grenoble Alpes, Grenoble, France

⁵Division of Neurology, Department of Neuroscience, Geneva University Hospitals, Geneva, Switzerland

Correspondence

Raul Martínez-Fernández, MD, PhD,
CINAC-University Hospital HM Puerta del Sur,
Av. Carlos V 70, 28938 Móstoles, Madrid,
Spain.
Email: rmartinez.hmcinac@hmhospitales.com

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Abstract

Parkinson's disease impairs the decoding of emotional stimuli reflecting alterations of the limbic cortico-subcortical network. The objective of this study was to assess and compare the behavioral and electrophysiological effects of both levodopa and subthalamic stimulation on emotional processing in Parkinson's disease. Operated patients ($n = 16$) and matched healthy subjects performed an emotional Stroop task, in which the emotion expressed by a face must be recognized while ignoring an emotional distractive word and that includes a neutral control sub-task. Patients were tested in the four possible treatment conditions (off stim/off med; on stim/off med; off stim/on med; and on stim/on med). High-resolution electroencephalography was recorded while performing the task. Patients made significantly more mistakes in facial emotion recognition than healthy subjects ($p < .005$). Untreated patients performed worse in the emotional trials than in the control sub-task ($p < .05$). Fearful faces induced significantly slower reaction times than happy faces in patients ($p = .0002$), but not in the healthy subjects. The emotional Stroop effect with levodopa was significantly higher than with subthalamic stimulation when fearful faces were assessed ($p = .0243$). Conversely, treatments did not modulate the Stroop effect of the control sub-task. EEG demonstrated that, compared with the untreated state, levodopa but not subthalamic stimulation significantly increases the amplitude of the event-related potential N170 ($p = .002$ vs. $p = .1$, respectively), an electrophysiological biomarker of early aspects of facial processing. The activity of the N170 cortical sources within the right fusiform gyrus was increased by levodopa ($p < .05$) but not by stimulation. While levodopa normalizes the recognition of emotional facial expression and early EEG markers of emotional processing, subthalamic stimulation does not. Thus, operated patients require dopaminergic medication in addition to stimulation to treat emotional symptoms of Parkinson's disease.

KEYWORDS

electroencephalogram, emotional conflict, emotional Stroop, levodopa, Parkinson's disease, subthalamic deep brain stimulation

1 | INTRODUCTION

Due to their high frequency and impact on patient's quality of life, the nonmotor symptoms of Parkinson's disease have gained much

attention in the last few decades, particularly mood manifestations such as apathy, depression, and anxiety (Benito-Leon, Cubo, & Coronell, 2012; Schrag, 2006). Parkinson's disease patients also suffer from emotional processing defects like impaired facial expression or prosody recognition, especially for negatively valenced emotions (Dujardin, Blairy, Defebvre, Duhem, et al., 2004a; Peron, Dondaine, Le Jeune, Grandjean, & Vérin, 2012). These emotional impairments are mediated by dopaminergic mechanisms (Sprengelmeyer et al., 2003)

Martínez-Fernández Raul and Kibleur Astrid contributed equally to this study.

Abbreviations: ACC, anterior cingulate cortex; DBS, deep brain stimulation; EEG, electroencephalogram; fMRI, functional magnetic resonance imaging; RT, reaction time; STN, subthalamic nucleus

and specifically, by dopaminergic denervation of the mesocorticolimbic pathway (Loulot & Besson, 2000; Tessitore et al., 2002), one of the functional cortico-subcortical basal ganglia loops (Obeso et al., 2008) that projects to limbic cortical areas involved in the pathophysiology of mood disturbances (Bishop, Duncan, Brett, & Lawrence, 2004; Kumari et al., 2003) or emotional conflict processing (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006; Whalen et al., 1998). In summary, in the same way that dopamine depletion of the nigrostriatal pathway drives parkinsonian motor features, the lack of dopamine in the mesolimbic loop would account for nonmotor psychic manifestations (Thobois, 2006; Thobois et al., 2010), including disturbances in emotional decoding (Castrìoto, Thobois, Carnicella, Maillet, & Krack, 2016; Tessitore et al., 2002).

Deep brain stimulation of the subthalamic nucleus (STN DBS) improves levodopa-sensitive motor features of Parkinson's disease (Krack et al., 2003; Limousin et al., 1998). However, the mood and behavioral changes after surgery remain somewhat unclear, as does the influence of STN DBS on the affective domain of Parkinson's disease (Castrìoto, Lhommée, Moro, & Krack, 2014). While several studies comparing patients before and after surgery highlight a further deterioration in facial emotion and prosody recognition (Aiello et al., 2014; Biseul et al., 2005; Drapier et al., 2008; Dujardin, Blairy, Defebvre, Krystkowiak, et al., 2004b; Le Jeune et al., 2008; Peron, Biseul, et al., 2010a; Peron, Grandjean, et al., 2010b; Vicente et al., 2009), others found no such effect of STN DBS (Albuquerque et al., 2014; McIntosh et al., 2014). Likewise, while enhanced mood and emotional processing has been reported (Bruck, Wildgruber, Kreifelts, Krüger, & Wächter, 2011; Castner et al., 2007; Schneider et al., 2003), so has worsening (Schroeder et al., 2004; Serranova et al., 2011) or no change (Berney et al., 2007). It is, therefore, difficult to draw definite conclusions given the methodological differences between studies. Nevertheless, behavioral changes have been reported after STN DBS (Castrìoto et al., 2014) and considering the anatomic overlap of the functional STN subdivisions (Haynes & Haber, 2013), stimulating the dorsolateral motor region of the STN may have some effects on the mesolimbic basal ganglia loop (Castrìoto et al., 2014).

A suitable way to explore emotional processes is through tasks that involve exposure to affective stimuli. In a modified version of the classic Stroop test (MacLeod, 1991) developed by Etkin et al. (2006), the facial emotional Stroop test, subjects are asked to recognize the emotion expressed by faces while ignoring the emotion of a word written over them. The difference in reaction times (RTs) between congruent and incongruent trials is named the Stroop effect, and it represents a measure of the overall conflict processing (Algom, Chajut, & Lev, 2004; Etkin et al., 2006). Thus, as both the task-relevant and the task-irrelevant stimuli involve emotional dimensions, the facial emotional Stroop allows studying modulation of attentional selection processes for emotional information. The same group designed a variant of the test by adding nonemotional trials in which subjects had to identify the gender of the faces with neutral emotional expression (Egner, Etkin, Gale, & Hirsch, 2008). Hence, while lateral prefrontal cortex was shown to resolve nonemotional conflict, the rostral ACC was involved in emotional conflict resolution. On the contrary, the detection of both types of conflict activated a common region of the dorsal ACC. Indeed, an amount of data from functional neuroimaging

studies shows that areas such as the rostral ACC, the amygdala, and orbito-frontal cortex are intimately linked to emotional processing (Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012). Specifically, a fMRI study with Parkinson's disease patients performing the emotional Stroop task showed that the resolution of emotional conflict depends on the integrity of the mesocortical dopamine projections, with dopamine modulating conflict resolution by normalizing the metabolism of the rostral ACC, which is hypoactive in the OFF drug state relative to the ON drug state and to healthy subjects (Fleury et al., 2014). Thus, these findings match with the hypothesis that the degeneration of the dopaminergic mesocortical circuit projecting to limbic areas underlies emotional disturbances and psychic nonmotor features of Parkinson's disease (Thobois et al., 2010) and, hypothetically, dopamine replacement therapy should help improve emotional processing and neuropsychiatric symptoms (Thobois et al., 2013). On the other hand, the potential modulation in emotional performance of STN DBS targeting the subthalamic motor region would depend on the impact of the stimulation field spreading to limbic STN areas.

Analysis of fMRI event-related activity is limited by the coarse temporal resolution of this technique (Dale & Halgren, 2001) and its restraints in patients who have undergone DBS. By contrast, high-density EEG ensures a neural signal with the highest temporal resolution and with an anatomic resolution of a few millimeters'. Indeed, EEG is being increasingly used to track emotional performance not only in healthy subjects but also in Parkinson's disease (Yuvaraj et al., 2014). Moreover, DBS artifacts on scalp recordings can be removed from EEG signals using adapted filtering techniques (Yvert, Perrone-Bertolotti, Baciú, & David, 2012). Thus, EEG recordings can be performed with DBS switched-ON and -OFF, which enables the interaction of DBS with the neural networks that underlie a subject's performance to be estimated from the evoked responses. Indeed, in a first EEG-DBS study of the emotional Stroop task, we recently showed how DBS of the sub-genual cingulate gyrus modulates the recorded event-related potentials in patients with depression (Kibleur et al., 2017). The highest amplitude evoked potential, thought to represent facial integration, corresponds to a negative infero-temporal deflection (N170) occurring around 170 ms after the presentation of a facial visual stimulus (Feuerriegel, Churches, Hofmann, & Keage, 2015; Hinojosa, Mercado, & Carretie, 2015; Vuilleumier & Pourtois, 2007). The amplitude of the N170 is known to be modulated by the emotional content of facial expressions (Hinojosa et al., 2015) and its generating areas include the fusiform gyrus, that encompasses the fusiform face area (Berchio et al., 2016; Nagy, Greenlee, & Kovacs, 2012). Indeed, this event-related potential is considered a biomarker of facial recognition deficits in neurological disorders including Parkinson's disease (Feuerriegel et al., 2015).

The aim of this study was to investigate how STN DBS and levodopa modulate behavior and cortical networks during emotional conflict processing in Parkinson's disease. As such, a group of STN DBS Parkinson's disease patients and matched healthy controls performed the emotional Stroop task while high-resolution EEG was recorded. From a clinical perspective, by disentangling the effects of both levodopa and stimulation in emotional aspects of PD this study will help to improve the management of the neuropsychiatric features of Parkinson's disease in operated patients.

2 | MATERIALS AND METHODS

2.1 | Patients

About 16 Parkinson's disease patients were recruited at the Neurology Department of the University Hospital of Grenoble, all fulfilling the UK Parkinson's Disease Society Brain Bank clinical criteria for Parkinson's disease (Hughes, Ben-Shlomo, Daniel, & Lees, 1992). All the patients had undergone bilateral STN DBS in the last 3 years and at least 3 months prior to enrolment.

Patients with dementia as defined by a score of $\leq 130/144$ in the Mattis dementia rating scale (Mattis, Bellak, & Karatsu, 1976); with severe frontal dysexecutive syndrome, with a score $\leq 30/50$ in the frontal score (Dubois & Pillon, 1997); suffering from moderate to severe depression, defined by a score >20 in the Beck depression inventory (Beck, Steer, Ball, & Ranieri, 1996); or with current impulse control disorder or psychotic manifestations were excluded. Neuropsychological evaluation was performed in the ON medication/ON stimulation state. The experimental task was also evaluated in 16 age and gender matched healthy subjects, with no active neuropsychiatric condition or cognitive impairment (evaluated through a directed interview for possible psychotic symptoms, the Beck depression inventory and the Mattis dementia rating scale). All patients and controls were native French speakers. The Ethics Committee of the Grenoble University Hospital approved this study (No. ID RCB 2014-A01392-45) and all the participants gave their written informed consent prior to enrolment.

2.2 | Surgery and electrode location

All Parkinson's disease patients were implanted bilaterally with two quadripolar Medtronic-3389 electrodes, targeting the dorso-lateral motor sub-region of the STN, and the electrodes were connected to a Kinetra or Activa stimulator (Medtronic, Minneapolis, Minnesota). The electrode positions were reconstructed in each patient using the Lead DBS toolbox (Horn & Kuhn, 2015), with individual pre- and post-operative T1 MRI and Advanced Normalization Tools normalization to the Montreal Neurological Institute space.

2.3 | Emotional Stroop task

In the emotional Stroop task, individuals attempted to recognize the emotion expressed by fearful or happy faces (emotional sub-task) while ignoring the superimposed words "JOIE" and "PEUR" ("happiness" and "fear" in French; Figure 1). It includes a control sub-task (nonemotional) where the subjects had to recognize the gender of neutral faces with the words "FEMME" and "HOMME" ("woman" and "man") superimposed on the pictures as the distractor. This paradigm was adapted from Etkin et al. (2006) and it has been detailed previously (Fleury et al., 2014; Kibleur et al., 2017). Each sub-task (emotional and control) was presented in two blocks of 200 stimuli (Figure 2). Following a cross-over design to compensate for possible learning effects, eight patients and eight healthy subjects started with the control sub-task, while the other 16 subjects started with the emotional sub-task. Subjects underwent a control training session

FIGURE 1 Emotional Stroop task: Stimuli for both sub-tasks (control and emotional), showing incongruent (with the distractor word and face valence having opposite meanings) and congruent (with the same valence for the distractor and the face) trials. Patients were asked to ignore the word and recognize the valence of the face (either woman vs. man in the control sub-task, or happy vs. scared in the emotional sub-task) and to click accordingly on the right or left button of a computer mouse [Color figure can be viewed at wileyonlinelibrary.com]

(with neutral faces) immediately prior to the experiment. The pictures of faces (neutral, fearful, and happy) were drawn from the Karolinska database (Lundqvist, Flykt, & Öhman, 1998), converted into gray scale using normalized histograms and contoured by an ellipsoid mask. The words were written in red capital letters using Arial font at size 60 in the center of each picture. The task was run on E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA), presenting congruent and incongruent trials in a pseudorandom order, and counterbalancing the gender to prevent anticipation effects. Participants were instructed to respond as fast and as accurately as possible by clicking on a mouse (either right or left mouse button), whether facial

FIGURE 2 Electrodes location: Top view of the electrodes repositioned over a STN atlas (Accolla et al., 2014) using the lead DBS toolbox for the 16 patients included. The active contacts are highlighted in red and the STN volume is color-coded according to the STN territories. Note, the active electrodes are consistently in the motor region (red) and none are positioned in the limbic region (yellow) [Color figure can be viewed at wileyonlinelibrary.com]

expressions expressed fear or happiness (or corresponded to a male or a female in the control sub-task).

2.4 | Experimental procedure

Data from each subject was acquired on the same day. The EEG helmet was placed on the subjects' head on arrival at the EEG facility and the study had a three-factor plan: (1) "Stroop sub-task" factor, either emotional or control; (2) "Levodopa" factor in function of levodopa administration (ON) or withdrawal (OFF); and (3) "STN DBS" factor as a function of the stimulation being switched ON or OFF. This allowed the task to be assessed in four treatment conditions: (1) OFF stimulation/OFF medication (OFF/OFF), (2) ON stimulation/OFF medication (ON DBS/OFF levodopa), (3) OFF stimulation/ON medication (OFF DBS/ON levodopa), and (4) ON stimulation/ON medication state (ON/ON). The OFF medication state was defined as overnight (≈ 12 hr) medication withdrawal, whereas the ON medication state was achieved after intake of a supramaximal levodopa dose (150–200% of the usual early morning dose for each patient, calculating the levodopa-equivalent dose according to a previously published formula (Lamberti et al., 2016). The ON drug state was defined as soon as both the neurologist and patient agreed that the best ON state had been reached. The OFF stimulation state was defined as a 30–45 min washout time after switching off the battery. ON stimulation parameters were not modified with respect to the chronic stimulation of the patient, considering that those had been optimized to treat motor features and therefore, they were more focused in the dorsolateral STN motor region. The two first task sessions were performed in the same order (OFF/OFF followed by ON DBS/OFF levodopa) so that the 12 hr dopaminergic drug withdrawal and the experiment could be run on a single day. The third and fourth trial conditions (OFF DBS/ON levodopa and ON/ON) were randomized. For healthy subjects the number of sessions was doubled to ensure a motivational modulation closer to that of the patients.

2.5 | Electroencephalography

Recordings were performed at the EEG research facility of Grenoble University Hospital. High-density 96 active electrode EEG (ActiCap, Brain Products, Germany) was used and the EEGs were recorded at a sampling rate of 2,500 Hz. Two additional electrodes were used to measure the electrooculograms for subsequent blink correction and two more electrodes were placed next to the DBS leads on the neck to measure stimulation artifacts. Six electrode (Fp1, Fp2, P3, P4, Cz, and Oz) positions on the head of each subject were measured relative to three fiducial points (nasion, left, and right tragus) using manual calipers, and the other electrode positions were interpolated from these measures using an ad hoc procedure derived from (Koessler et al., 2007). Reference and ground were taken at FCz and AFz, respectively.

2.6 | Statistical analysis and EEG processing

Behavioral results were entered into an ANOVA analysis, with random effects on the patients' factor, and the other factors being DBS (either

"ON" or "OFF"), levodopa (either "ON" or "OFF"), congruency (either congruent or incongruent) and emotional valence (either control "CTRL" or emotional "EMO"). Post-hoc paired *t*-tests on contrasts of interest were run to refine the analyses: parametric classical *t*-tests were used for the RTs (normally distributed) and non-parametric test for the non-normally distributed accuracy data. For the intergroup (patient vs. healthy subjects) comparisons, two sample *t*-tests parametric (for the RTs) and non-parametric (for the accuracy) were used. Finally, correlations between behavioral measures (RTs and accuracy) and clinical data (medication dose, UPDRS, etc.) were tested using the *corrcoef* function from the statistical toolbox from Matlab.

The EEGs were preprocessed with EEGLAB (Delorme & Makeig, 2004), and statistical analyses and source reconstruction were performed using Statistical Parametric Mapping software (SPM12, Wellcome Trust Centre for Neuroimaging, <http://www.fil.ion.ucl.ac.uk/software/spm12/>). EEG signals were first filtered between 0.5 and 40 Hz in EEGLAB (1,651 points order FIR default filter from the 2,500 Hz recording data), and downsampled to 250 Hz. An independent component analysis was then used to remove blink artifacts (determined using the topographical and spectral components) and an average reference montage was applied. EEG signals were epoched between –500 and 1,000 ms, peristimuli and baseline corrected. Scalp event-related potentials were obtained by averaging together the trials of the same condition, after removing trials with high noise levels. Analysis was focused on the N170 given its well-known sensitivity to facial expression (Hinojosa et al., 2015) and on our recent results on its dependency on stimulation of the sub-genual cingulate cortex in the same task (Kibler et al., 2017). Moreover, this potential had the higher Signal to Noise ratio in our recordings (compared with the P100 or the P300 for instance), therefore, its modulation by the task conditions where sharper than the other potentials. To compute the N170 waveform, the EEG signals were averaged over 15 occipital-temporal electrodes chosen for each patient, and showing the highest amplitude (negative peak) between 120 and 220 ms.

Source reconstructions were only computed for the emotional Stroop sub-task as event-related potentials were not modulated by treatments in the control sub-task. A SPM12 greedy search approach was used with group inversion using the head model built with the Boundary Element Method based on the T1 MRI images for each subject. The cortical current density images were entered into a $4 \times 2 \times 2$ ANOVA statistical design with the three factors being: the four treatment conditions (with covariates linking each patient treatment condition), the emotional expression of the faces (joy or fear), and the stimuli congruency (either congruent or incongruent).

3 | RESULTS

3.1 | Patients

The clinical characteristics of the 16 Parkinson's disease patients studied (seven males and nine females, with a mean age of 59 ± 9 years: range 36–70) are shown in Table 1. Healthy subjects were matched for age and gender (seven males and nine females, with a mean age of

TABLE 1 Patient's demographic characteristics

P	Sex	Age (y)	Duration of PD (y)	Fluctuations onset	Time from DBS (months)	Mattis DRS (/144)	UPDRS III				Levodopa equivalent dose administered
							OFF OFF	ON OFF	OFF ON	ON ON	
1	M	60	10	2008	14	136	36	11.5	4.5	3	165
2	F	71	10	2008	14	141	33.5	17.5	9	9	250
3	F	66	10	2012	4	141	35	13	13.5	7.5	200
4	F	69	14	2001	26	135	53.5	24	19	17	125
5	M	63	12	NA	16	140	55	26	13.5	10	300
6	F	62	12	2011	6	136	34	16.5	6	5.5	225
7	M	65	19	2008	7	141	38.5	20	10.5	10	250
8	F	50	9	NA	11	141	32	14	8	4	200
9	M	60	12	NA	6	131	48	24	20	17	300
10	F	54	6	2011	4	143	35	25.5	10	7	200
11	F	36	8	2009	3	140	24	13	10	4	200
12	F	64	10	2007	12	136	21.5	13	9	7	200
13	M	50	5	2011	20	144	31.5	13.5	11	11	300
14	F	56	9	2010	20	144	22	17	13	11	250
15	M	51	6	2012	3	137	60	27	12.5	11	200
16	M	68	9	NA	12	139	47	24	21	14	200

P = patient; PD = Parkinson's disease; DBS = deep brain stimulation; DRS = dementia rating scale; UPDRS, Unified Parkinson's Disease Rating Scale; M = male; F = female; NA = not available.

59 ± 10 years; range 33–70). All patients suffered from pre-operative motor complications, which were the indication for surgery.

3.2 | Electrode location

The active electrodes were those providing the best motor and they were systematically located within or very close to the motor region of the STN (Figure 2), as seen by electrode repositioning in a STN atlas (Accolla et al., 2014).

3.3 | Behavioral data

3.3.1 | Intergroup comparison for accuracy and reaction time

When analyzing all the sessions, correct responses were given for 85.5 ± 2.3% (for the emotional sub-task in the OFF/OFF condition) to 94.9 ± 0.9% (for the control sub-task in healthy subjects) (results are described in Table 2). Parkinson's disease patients made significantly more mistakes than healthy subjects, especially in the emotional sub-task ($p < .005$, Wilcoxon rank sum test), whereas the difference between these two groups was not significant in the control blocks ($p = .179$, Wilcoxon rank sum test). Patients showed a trend toward higher RTs than healthy subjects in the recognition of fearful faces ($p = .08$).

3.3.2 | Intragroup comparison for accuracy and reaction time

In the OFF/OFF state, patients made significantly more mistakes in the emotional trials than in the control trials ($p = .0063$, Wilcoxon rank sum test), a difference that was not found in any other treatment condition nor in the healthy subjects.

Levodopa had a significant effect on the RT and Parkinson's disease patients were significantly quicker after receiving levodopa than without medication (733.5 vs. 775 ms respectively; $p = .003$). Furthermore, there was significant interaction effect between levodopa and DBS, where the levodopa effect on RTs (decrease) was significantly weaker when DBS was ON than when DBS was OFF (7.6 vs. 75.5 ms, respectively; $p = .0008$). RT was not reduced significantly by DBS alone.

Specifically, in the emotional blocks, both DBS and levodopa significantly decreased the RT (773.2 ms for OFF DBS conditions vs. 746.0 ms with ON DBS; 784.4 ms OFF levodopa vs. 734.8 ms ON levodopa; $p = .0008$ and $p = .0025$, respectively). Moreover, the interaction effect between levodopa and DBS was also significant (levodopa effect OFF DBS, 75.6 vs. 23.6 ON DBS; $p = .0015$). In Parkinson's disease patients, fearful faces induced significantly slower RTs than joyful faces (RT fear = 781.8 ms, RT joy = 737.5 ms; $p = .0002$), whereas this was not the case in the healthy subjects (723.8 ± 23.5 ms vs. 737.0 ± 19.6 ms, respectively, $p = .232$). Moreover, in the healthy subjects group there was no significant difference in RT and accuracy between the emotional and the control subtask.

We found no significant correlation between the performance (accuracy and RT) in the OFF DBS/OFF levodopa condition and the patients' age, time from DBS or UPDRS score ($p > .1$). No correlation was found between the administered levodopa dose and patients' performance in either the ON DBS/ ON levodopa ($p > .6$) or the OFF DBS/ON levodopa conditions ($p > .4$).

3.3.3 | Stroop effect

There were significantly longer RTs for incongruent than for the congruent trials under all experimental conditions (Table 3, A) RT for ICG trials = 790.2 ms, RT for CG trials = 718.3 ms; $p < .0001$), meaning a robust positive Stroop effect. Moreover, when the emotional sub-task

TABLE 2 Descriptive behavioral results of the emotional Stroop task

Measure	Treatment condition				
	OFF stim	ON stim	OFF stim	ON stim	Healthy subjects
	OFF med	OFF med	ON med	ON med	
Accuracy (%)					
Emotional subtask	85.5 ± 2.3	89.1 ± 3.3	87.8 ± 2.0	88.9 ± 1.4	94.9 ± 0.7
Control subtask	89.6 ± 2.1	93.4 ± 1.8	89.7 ± 1.6	90.5 ± 2.0	94.9 ± 0.9
Reaction time (ms)					
Emotional subtask	810.6 ± 23.9	756.4 ± 20.5	735.2 ± 16.6	733.3 ± 19.2	754.9 ± 30.8
Control subtask	788.3 ± 23.8	744.9 ± 21.5	712.6 ± 17.0	752.9 ± 40.3	746.5 ± 28.5
Stroop effect (ms)					
Emotional subtask	61.5 ± 9.8	45.4 ± 10.7	80.2 ± 13.4	72.8 ± 11.0	77.4 ± 12.7
Control subtask	73.7 ± 12.4	71.9 ± 15.1	77.5 ± 12.4	92.7 ± 19.3	58.6 ± 7.9

was considered alone (Table 3, B), the RT for ICG trials was also significantly longer than for CG trials (792.2 vs. 727 ms, respectively; $p < .0001$).

There was no significant difference in the magnitude of the emotional Stroop effect between healthy subjects and patients, regardless of treatment condition.

Among patients, no differences between conditions were found in the Stroop effect for the control sub-task. Conversely, the Stroop effect for the emotional sub-task tended to be larger under dopaminergic treatment alone than exclusively under stimulation (OFF DBS/ON levodopa = 80.2 ± 13.4 ms, ON DBS/OFF levodopa = 45.4 ± 10.7 ms; $p = .0547$ paired t test). If only fearful faces were considered, the

difference in the Stroop effect between both conditions became significant (OFF DBS/ON levodopa = 85.9 ± 14.3 ms, ON DBS/OFF levodopa = 44.1 ± 10.7 ms; $p = .0243$). Conversely, there were no significant differences when comparing the other treatment conditions for either the total emotional Stroop effect (OFF/OFF = 61.5 ± 9.8 ms, ON/ON = 72.8 ± 11.0 ms) or that of fearful faces (OFF/OFF = 52.8 ± 11.4 ms; ON/ON = 77.1 ± 11.7 ms).

3.4 | Event-related potentials

First, we did not find significant difference between N170 amplitude between patients in the OFF/OFF condition and healthy subjects (−6.71 vs. −7.42 μ V, $p = .61$). In the intragroup (patients) comparison, no significant effects of the treatments on the amplitude of N170 were found for the control sub-task. On the other hand, for the emotional trials levodopa significantly increased the N170 amplitude, from −6.45 μ V OFF levodopa to −7.5 μ V ON levodopa ($p = .0025$), whereas DBS did not significantly affect this parameter (from −7.3 μ V OFF DBS to −6.7 μ V ON DBS, $p = .1$). Main findings on the N170 for emotional trials are presented in Table 4 and Figure 3. In addition, an effect of congruency was evident, with incongruent trials eliciting a lower N170 amplitude than congruent trials (−6.78 μ V for incongruent trials and −7.19 μ V for congruent trials; $p = .009$). Moreover, there was a significant interaction effect of levodopa and congruency (OFF levodopa = 0.03 μ V; ON levodopa = 0.74; $p = .0084$; Figure 3c). Finally, the interaction between levodopa and emotional valence was

TABLE 3 Significant effects ($p < .05$) on reaction times (A: Total, for both emotional and control subtasks; B: for emotional subtask only)

(A) Factor		RT (ms)	F	p
Congruency	Incongruent trials	790.26	74.03	<.00001
	Congruent trials	718.28		
Levodopa	OFF	775.06	11.91	.003
	ON	733.48		
DBS × levodopa (RT levodopa OFF–RT levodopa ON)	DBS OFF	75.55	17.47	.0008
	DBS ON	7.61		
Levodopa × congruency (SE)	Levodopa OFF	63.13	4.76	.454
	Levodopa ON	80.82		
(B) Factor		RT (ms)	F	p
Congruency	Incongruent trials	792.23	85.23	<.00001
	Congruent trials	727.01		
Valence	Positive valence (happy faces)	737.47	24.61	.0002
	Negative valence (fearful faces)	781.77		
Levodopa	Levodopa OFF	784.42	13.18	.0025
	Levodopa ON	734.82		
DBS	DBS OFF	773.25	17.5	.0008
	DBS ON	745.99		
DBS × levodopa (RT levodopa OFF–RT levodopa ON)	DBS OFF	75.65	15.01	.0015
	DBS ON	23.57		

RT = reaction time; DBS = subthalamic nucleus deep brain stimulation; SE = Stroop effect (i.e., incongruent RT–congruent RT).

TABLE 4 Significant effects ($p < .05$) on the N170 amplitude for the emotional trials

Factor		Amplitude differences (μ V)	F	p
Congruency	Incongruent trials	−6.78	9.06	.009
	Congruent trials	−7.19		
Levodopa	OFF	−6.45	13.16	.0025
	ON	−7.50		
Levodopa × congruency (SE)	Levodopa OFF	0.03	9.2	.0084
	Levodopa ON	0.74		
Levodopa × valence (RT levodopa OFF–RT levodopa ON)	Negative valence (fearful faces)	0.76	7.79	.0137
	Positive valence (happy faces)	1.35

FIGURE 3 The occipital N170 in the emotional condition. (A) Mean event-related potential amplitude in the occipito-temporal region in healthy subjects (from the 15 electrodes for each subject with the highest amplitude in the time interval [100–240] ms). The shaded area represents the SEM (across subjects). (B) Topography of the N170 averaged over the time interval [140–200] ms; (C) comparison of the difference in N170 amplitude between the incongruent and congruent trials (i.e., the electrophysiological representation of the magnitude of the Stroop effect): (a) for the OFF DBS (in red) and ON DBS states (in blue); (b) for the OFF levodopa (in blue) and ON levodopa states (in red); (c) for the ON levodopa (in red) and ON DBS states (in blue). As shown in C(a) and C(b) the amplitude of the difference in the peaks of the N170 in the two conditions of congruency is significantly modulated by levodopa but not by DBS [Color figure can be viewed at wileyonlinelibrary.com]

also significant, as the levodopa effect (increase in amplitude) was 0.76 μV for fearful faces and 1.35 μV for happy faces ($p = .01$). Moreover, for the later event-related potentials, the N270 and P450, no significant differences on the peak amplitude were evident between levodopa and STN DBS ($p > .05$).

3.5 | EEG source reconstruction

Reconstruction of the EEG source in healthy subjects established a reference for the regions involved in the emotional sub-task at different time intervals: 170, 270, and >500 ms (Figure 4). The source analysis was restricted to the emotional sub-task in Parkinson's disease patients, and during the N170 component, DBS decreased the activity in the fusiform gyrus and the lateral temporal cortex, especially in the right hemisphere (Figure 5a). Conversely, levodopa increased the activity in the posterior inferior temporal cortex, including the fusiform face area and the lateral occipital face area of the right hemisphere (Figure 5b). Neither levodopa nor DBS elicited significant modulation 250 ms after the onset of the stimulus. When studying the contrast between congruent and incongruent emotional stimuli (i.e., the electrophysiological activity underlying the emotional Stroop effect), there was a significant decrease in activity of the bilateral temporal poles in Parkinson's disease patients without levodopa, even in the fusiform area (Figure 6b). However, the pattern of activation more

closely approximated to that of healthy subjects with levodopa ON (Figure 6c).

4 | DISCUSSION

In this study we found that: (1) Parkinson's disease patients made significantly more mistakes than healthy subjects in the recognition of emotional facial expressions; (2) Parkinson's disease patients OFF treatment were less accurate in the emotional sub-task than in the control sub-task; (3) Parkinson's disease patients were slower than healthy subjects in the recognition of fearful facial emotions and they were slower in recognizing faces conveying fear than expressions of happiness; (4) For fearful facial expressions, the amplitude of the Stroop effect was significantly larger under levodopa therapy than with DBS alone while the treatments did not modify the Stroop effect in the control sub-task; (5) The N170 peak amplitude was increased by levodopa but not by STN DBS, with significant differences in the amplitude of potentials between both conditions; (6) The difference in the N170 amplitude between incongruent and congruent emotional trials increased significantly after levodopa therapy but not with DBS; and (7) Source reconstructions applied to the emotional sub-task indicated that this effect was associated with levodopa driving stronger activity in the right fusiform gyrus (a cortical source of the N170), whereas DBS elicited hypoactivation of the same region.

FIGURE 4 T maps ($p < .05$) of the source reconstruction of the healthy control group at different time intervals: (a) 140–200 ms, the infero-temporal cortex that includes visual temporal areas and the fusiform gyrus shows the strongest activation, particularly in the right hemisphere; (b) 200–330 ms the strongest activity was found in the medio-central gyri and parietal cortex, as well as in the anterior temporal pole, while activity in the infero-temporal cortex remained strong; and (c) 500–600 ms there was a reduction in the activity of the regions implicated, even in the inferior temporal regions, while frontal areas remained activated. The regions with the strongest activation are in yellow [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 5 T maps ($p < .05$) of the source reconstruction showing the different effects of STN DBS and levodopa on cortical EEG 140–200 ms after the emotional stimuli. (a) The effect of DBS (contrast: ON DBS–OFF DBS). (b) The effect of levodopa (contrast: ON levodopa–OFF levodopa). Activated regions in yellow/red; deactivated regions in blue [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 6 Source reconstruction representation of the emotional Stroop effect in the time interval 140–200 ms: Contrast between incongruent and congruent trials ($p < .05$ uncorrected). (a) In healthy subjects, activation decreased in the left fusiform gyrus, the lateral occipital cortex, the temporo-parietal junction and the left prefrontal cortex in incongruent trials relative to the congruent trials. (b) Patients in the levodopa OFF state showed significant deactivation of the bilateral temporal lobes. (c) The Parkinson's disease patients in the levodopa ON state showed weaker activity in areas that included the lateral occipital areas and the left dorsolateral prefrontal cortex, with a similar pattern to healthy subjects and with a minor deactivation in the fusiform area. Activated regions in yellow/red; deactivated regions in blue [Color figure can be viewed at wileyonlinelibrary.com]

4.1 | Emotional processing disturbances in Parkinson's disease patients

Deficits in recognition and processing of different emotional modalities have frequently been reported in Parkinson's disease patients (Benke, Bosch, & Andree, 1998; Bowers et al., 2006; Gray & Tickle-Degnen, 2010; Jacobs, Shuren, Bowers, & Heilman, 1995; Peron, Frühholz, Ceravolo, & Grandjean, 2016; Peron et al., 2017; Schroder, Mobes, Schute, & Dengler, 2006). Two major mechanisms have been invoked to explain abnormal emotional processing in Parkinson's disease: dysfunction of the mesocorticolimbic basal ganglia circuit and the amygdala (Yoshimura, Kawamura, Masaoka, & Homma, 2005). Moreover, functional connectivity studies have demonstrated amygdalo-mesocorticolimbic connections (Etkin et al., 2006; Satterthwaite et al., 2011). According to functional neuroimaging studies, both the ventral striatum (main mesolimbic basal ganglia input) and the amygdala are involved in processing the negative emotions of fear

and disgust (Morris et al., 1996; Phillips et al., 1998). They share dopamine as a major neuromodulator and they consistently receive afferents from the dopaminergic neurons of mesolimbic ventral tegmental area, which are known to degenerate in Parkinson's disease.

In our study, Parkinson's disease patients demonstrated impaired emotional decoding and they were less accurate in recognizing emotional facial expression than healthy subjects, with this deficiency being partially compensated by levodopa intake as previously reported (Sprengelmeyer et al., 2003). In contrast to healthy subjects, Parkinson's disease patients responded more slowly and less accurately in the emotional trials than in the control trials, suggesting specific difficulties in processing emotional information. Indeed, faces expressing fear (i.e., negative emotions) were recognized more slowly by Parkinson's disease patients but not by healthy subjects. The impairment in specific recognition of negative emotions as opposed to positive ones has been frequently reported in Parkinson's disease (Gray & Tickle-Degnen, 2010; Mondillon et al., 2012). Moreover, this

disturbance has been shown to improve with the combination of STN DBS and levodopa, with this effect being related to the modulation of occipito-temporal activity (Mermillod et al., 2014), which are the regions where we found the highest modulation (N170 source generators).

4.2 | Effects of levodopa and STN DBS in modulating the emotional Stroop effect

Levodopa and stimulation modulated the emotional Stroop effect distinctly, whereas these treatments did not affect the control sub-task. When confronted with emotional faces, levodopa but not STN DBS tended to increase the magnitude of the Stroop effect relative to the OFF/OFF state. Furthermore, the difference in the size of the Stroop effect between ON DBS/OFF levodopa and OFF DBS/ON levodopa was significant when fearful faces were considered. A higher magnitude of the emotional Stroop effect with trials of faces expressing fear has been previously found for Parkinson's disease patients ON drug and healthy subjects relative to the OFF drug state (Fleury et al., 2014). Our results partially match these findings as the Stroop effect is stronger in magnitude in Parkinson's disease patients that received levodopa and in healthy subjects. By contrast to levodopa, STN DBS has no significant impact on emotional conflict processing. It has been shown that Emotional Stroops can be sensitive to the so-called "emotional dilution phenomenon" (Chajut, Schupak, & Algom, 2010; Reynolds & Langerak, 2015), where subject's impaired processing of the emotion decreases the conflict-based difference between congruent and incongruent trials. Thus, by improving emotion recognition and disengagement from the emotion of the face, levodopa would increase susceptibility to both the face and the word, reducing emotional dilution, and thus increasing conflict detection. Conversely, patients OFF levodopa would be more held by the saliency of facial emotional stimulus and, in consequence, emotional dilution would be higher as a result of the engagement of the patient to the salience of the emotional face (Muhlberger et al., 2009). Conversely, the selective effect of DBS on STN motor subregion would result in no significant behavioral modulation of emotional processing. Importantly, the performance in the earlier emotional facial expression recognition depending on treatment state would eventually impact on the subsequent processing of the emotional conflict. Indeed, the observed differences between ON DBS/OFF levodopa and OFF DBS/ON levodopa conditions in terms of Stroop effect might be a consequence of a primary deficit/improvement in facial emotion recognition rather than a modulation over the processing of emotional conflict itself. However, the effect of each treatment on the emotional recognition and the conflict processing can be disentangled by using ANOVA design and entering both experimental conditions as factors. Thus, after studying the interaction between the DBS or levodopa factor and the conflict factor we can assume an effect of treatments on conflict (i.e., Stroop effect magnitude).

Finally, the distractor did not induce higher rate of errors in the incongruent trials than in the congruent in any treatment condition. Moreover, more rapid RTs did not result in more errors neither in the levodopa ON condition nor in the DBS ON states, excluding a possible increase in impulsivity. Thus, the intragroup differences in the Stroop

effect between ON DBS/OFF levodopa and OFF DBS/ON levodopa might suggest that this measure, comprising a relevant stimulus and a distractor, requires higher processing and might be more sensitive to detect differences.

4.3 | The N170 as a marker of emotional facial detection

Only two studies have analyzed the N170 event-related potential in Parkinson's disease and no differences in N170 amplitude and peak delay relative to healthy subjects were found (Wieser et al., 2012; Yoshimura et al., 2005). However, both studies tested patients on regular dopaminergic medication and therefore, with the effect of dopamine depletion compensated.

Here, the N170 amplitude for the emotional sub-task was increased by levodopa but it was not modulated by STN DBS. In addition, levodopa amplified the difference in the N170 amplitude between incongruent and congruent trials (the electrophysiological representation of the Stroop effect), whereas stimulation did not. Interestingly, this modulation of the N170 by treatment was not found in the control sub-task. Moreover, EEG source reconstruction during the emotional sub-task demonstrated that levodopa increased the activity of the N170 generator regions, such as the fusiform face area (Nagy et al., 2012), while STN DBS hypoactivated them. This difference in brain regional activation by each treatment would be conveying distinct modulation of facial emotional recognition. Thus, the matching between our electrophysiological and behavioral results suggests the modulation of the emotional Stroop effect (i.e., emotional conflict processing) by levodopa but not by STN DBS, with this modulation being mainly mediated through the effect of each treatment on the recognition of facial emotion.

Visual cortical regions, and the fusiform gyrus in particular, have direct reciprocal projections to the threat-detector amygdala (Amaral & Insausti, 1992), which, in turn, is functionally related to mesocorticolimbic areas such as the ACC. Indeed, a correlation between amygdala activation and fusiform gyrus activity has been demonstrated when confronted by fearful faces (Morris et al., 1998; Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004). Due to neuronal damage and dopamine depletion, the amygdala is relatively silent after fear stimuli in Parkinson's disease (Tessitore et al., 2002; Yoshimura et al., 2005). Despite EEG could not analyze amygdala and ACC activity due to its deep anatomical location, we hypothesize that reduced N170 potentials in patients that have not received levodopa and deactivation of the fusiform gyrus might ultimately represent functional consequences of amygdala/mesocorticolimbic network dysfunction. Levodopa has a global and relatively widespread effect on the brain, yet it could partially restore the function of the amygdala (Tessitore et al., 2002) and the whole mesocorticolimbic network (Fleury et al., 2014) and consequently, normalize fusiform gyrus activity and N170 amplitude. Alternatively, with DBS selectively targeting the dorso-lateral sensorimotor region of the STN, only a small amount of current will spread toward the limbic pathway. This may be insufficient to affect the early visual feedback system, thereby failing to modulate the N170 amplitude and underactivating the regions that generate it.

In summary, our data suggest that the deficit in integrating emotional facial expression and the subsequent conflict processing in

Parkinson's disease could be primarily caused by abnormal activity in the fusiform face area. Levodopa but not sensorimotor STN DBS can compensate for the weaker emotional feedback from mesocorticolimbic areas to facial expression decoding regions, impairing the processing of faces expressing fear. This finding is reflected by the altered Stroop effect and electrophysiologically, by the differences in N170 amplitude and the activity within the fusiform gyrus.

4.4 | Clinical considerations

Our results support that impaired detection of fearful facial expression could be mediated by a lack of dopamine in the mesocorticolimbic network. This situation might impede arousal activation upon exposure to an emotional stimulus, a typical feature of parkinsonian apathy that is characterized by emotional flattening and lack of autoactivation (Pagonabarraga, Kulisevsky, Strafella, & Krack, 2015). Two possible explanations might underlie the appearance of postoperative apathy: (i) the decrease in dopaminergic stimulation allowed by stimulation of the sensorimotor STN unmasking mesocorticolimbic denervation (Thobois et al., 2010); and (ii) stimulation per se inducing apathy by current diffusion to the non-motor STN (Drapier et al., 2006) based upon the observation that stimulation inhibits the normal emotional activation of the fusiform gyrus (Geday, Ostergaard, & Gjedde, 2006). However, the acute effects of STN DBS improve off-dysphoria (Funkiewiez et al., 2006) and apathy (Czernecki et al., 2005), arguing against this latter hypothesis. In the present study, levodopa enhanced activity in N170 generator regions, while STN DBS hypoactivated them. This opposing effect should not be overestimated but it might support the second hypothesis and revitalize this longstanding debate.

In contrast to apathy, dopaminergic stimulation in the Parkinson's disease damaged mesocorticolimbic system might increase alertness and enhance sensitivity toward emotions (Kulisevsky, Pagonabarraga, & Martínez-Corral, 2009). The supraliminal dose of levodopa administered in this study, could explain the improvement in emotional processing and the electrophysiological changes in the mesocorticolimbic regions of patients ON levodopa. This is clinically relevant and suggests that to compensate the dopaminergic depletion in mesocorticolimbic areas, dopaminergic medications are needed. This might explain why patients develop a neuropsychiatric hypodopaminergic syndrome when the decrease in dopaminergic treatment after STN DBS is too fast or too large (Thobois et al., 2010). Accordingly, reasonable maintenance dose of Parkinson's disease treatments after surgery might prevent the occurrence of neuropsychiatric symptoms, including emotional processing disturbances (Dujardin, Blairy, Defebvre, Krystkowiak, et al., 2004b; Thobois et al., 2010). Our results would be compatible with the postoperative improvements in neuropsychiatric complications recently demonstrated in a randomized controlled trial of STN DBS versus levodopa (Lhommee et al., 2018).

This experimental study has some limitations, such as the sample size, its heterogeneity in terms of the patient's clinical characteristics and the time since surgery. Moreover, the task was presented in all patients first in the ON medication state and secondly OFF Levodopa (with stimulation states randomized in the latter), which could result in a bias due to learning effect. However, the different modulation by treatments in the emotional sub-task was not found for non-emotional

faces, suggesting a real distinct impact of therapies specifically in the emotional processing. In addition, the stimulation volume was not defined and therefore, the "amount" of electrical current spreading to the STN limbic sub-region could not be measured or correlated to the behavioral and electrophysiological findings. Future studies of STN DBS for neuropsychiatric diseases targeting the non-motor STN, or current steering in Parkinson's disease covering both the motor and non-motor territories of the STN, may resolve this issue.

5 | CONCLUSION

Together, our findings confirm that Parkinson's disease patients suffer impairment in facial emotional recognition, particularly regarding fearful facial expressions. Temporospatial analysis using EEG during the emotional Stroop task reveals a dysfunction in the early processing of facial emotions. This defect could be anatomically localized to the infero-temporal cortex that is involved in visual recognition and discrimination, and to the fusiform gyrus that is responsible for the early integration of facial emotional information. While levodopa tends to normalize the Parkinson's disease-related impairment in early visual emotional processing, this is not the case with STN DBS. Unraveling the mechanisms underlying Parkinson's disease neuropsychiatric manifestations, and the effects and side effects of levodopa and STN DBS therapies, will contribute to optimize the management of behavioral disorders in Parkinson's disease patients.

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ORCID

Raul Martínez-Fernández <https://orcid.org/0000-0002-0305-013X>

Olivier David <https://orcid.org/0000-0003-0776-0216>

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