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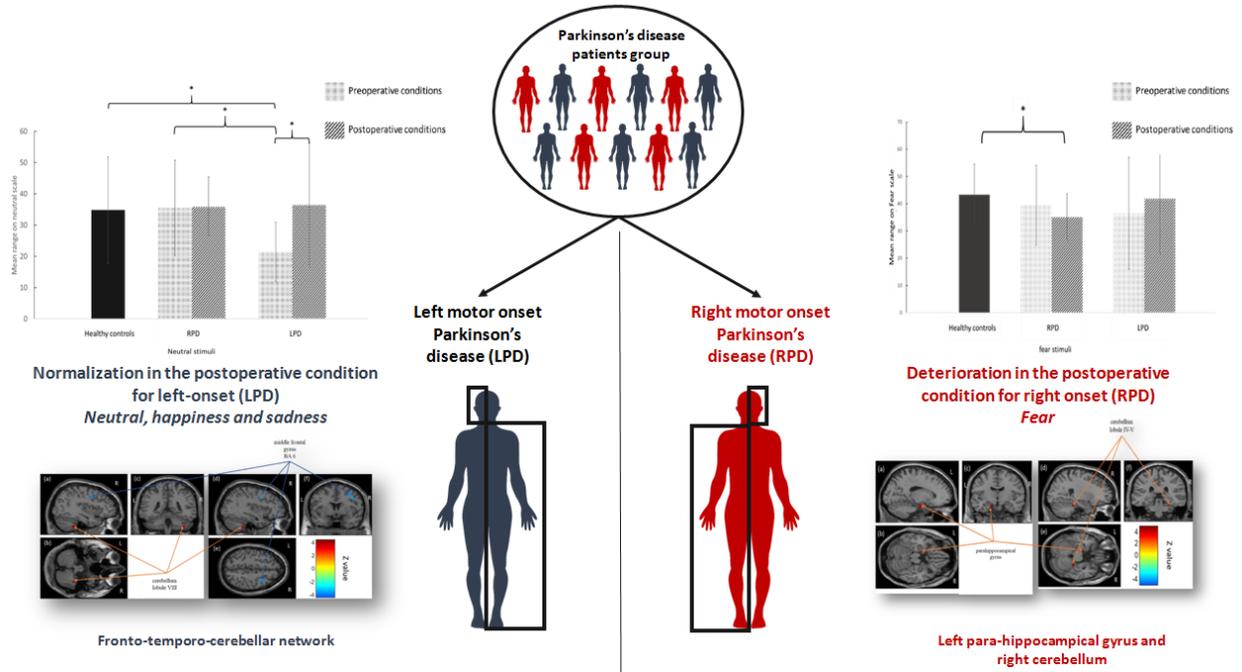
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1 Running head: Vocal emotion and STN DBS in PD

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3 **Motor symptom asymmetry in Parkinson's disease predicts emotional outcome**
4 **following subthalamic nucleus deep brain stimulation**

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42

43 **Conflict of interest**

44 The authors report no conflicts of interest.

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ABSTRACT

The objective of this study was to explore the brain modifications associated with vocal emotion (i.e., emotional prosody) processing deficits in patients with Parkinson's disease after deep brain stimulation of the subthalamic nucleus, and the impact of motor asymmetry on these deficits. We therefore conducted 18-fluorodeoxyglucose positron emission tomography scans of 29 patients with left- or right-sided motor symptoms of Parkinson's disease before and after surgery, and correlated changes in their glucose metabolism with modified performances on the recognition of emotional prosody. Results were also compared with those of a matched healthy control group. Patients with more left-sided motor symptoms exhibited a deficit in vocal emotion recognition for neutral, anger, happiness and sadness in the preoperative condition that was normalized postoperatively. Patients with more right-sided motor symptoms performed comparably to controls in the preoperative condition, but differed significantly on fear postoperatively. At the metabolic level, the improvement observed among patients with left-sided motor symptoms was correlated with metabolic modifications in a right-lateralized network known to be involved in emotional prosody, while the behavioral worsening observed among patients with right-sided motor symptoms was correlated with metabolic modifications in the left parahippocampal gyrus and right cerebellum. We suggest that surgery has a differential impact on emotional processing according to motor symptom lateralization, and interpret these results as reflecting the (de)synchronization of the limbic loop in the postoperative condition.

Keywords: emotional prosody, Parkinson's disease, asymmetry, striatum, ¹⁸FDG-PET, subthalamic nucleus, deep brain stimulation

69 **Abbreviations:** ANOVA, analysis of variance; BA, Brodmann area; DBS, deep brain
70 stimulation; ¹⁸F-DG-PET, 18-fluorodeoxyglucose positron emission tomography; FDR, false
71 discovery rate; fMRI, functional magnetic resonance imaging; GLMM, generalized linear
72 mixed model; HC, healthy control; H&Y, Hoehn and Yahr scale; IFG, inferior frontal gyrus;
73 LEDD, levodopa-equivalent daily dose; LPD, patients with Parkinson's disease exhibiting
74 predominantly left-sided motor symptoms; MADRS, Montgomery-Åsberg Depression Rating
75 Scale; MCST, Modified Wisconsin Card Sorting Test; MDRS, Mattis Dementia Rating Scale;
76 OFC, orbitofrontal cortex; PD, Parkinson's disease; RPD, patients with Parkinson's disease
77 exhibiting predominantly right-sided motor symptoms; S&E, Schwab and England scale;
78 SPM, statistical parametric mapping; STAI, State-Trait Anxiety Inventory; STN, subthalamic
79 nucleus; UPDRS, Unified Parkinson's Disease Rating Scale.

80

81 1 INTRODUCTION

82 Over the past decade, research on the emotional effects of subthalamic nucleus (STN)
83 deep brain stimulation (DBS) in patients with Parkinson's disease (PD) or
84 obsessive-compulsive disorder, coupled with intracranial recordings or metabolic functional
85 imaging, has enabled researchers to explore the STN's functional specialization and
86 integration in emotion (Le Jeune *et al.*, 2010; Péron, Frühholz, Vérin, & Grandjean, 2013;
87 Péron, Grandjean, *et al.*, 2010; Péron, Le Jeune, *et al.*, 2010). On the basis of this corpus of
88 findings, an integrative model has been developed (Péron *et al.*, 2013), according to which the
89 STN forms part of a distributed neural network underlying emotion processing in humans.
90 More specifically, rather than playing a specific function in a given emotional process, the
91 STN, together with other basal ganglia, coordinates neural patterns, either synchronizing or
92 desynchronizing the activity of the different neuronal populations involved in specific
93 emotion components. For the recognition of vocal expressions of emotion (*i.e.*, emotional
94 prosody), for instance, the basal ganglia recruit and synchronize the activity of the structures
95 involved in the different steps of emotional prosody processing, while competing neuronal
96 patterns are inhibited (Péron *et al.*, 2013). This mechanistic process subtends the ensuing
97 function. In line with Graybiel (2008)'s propositions concerning the motor and cognitive
98 domains, the basal ganglia iteratively assess contexts and select actions in order to form (or
99 control the expression of) coordinated emotional sequences. If these emotional sequences
100 become recurrent or repetitive, the basal ganglia combine their representations into units (also
101 called *chunks*). In other words, the basal ganglia code for the neuronal co-activation of the
102 different cortical and subcortical structures needed for specific emotion components, in order
103 to chunk information into manageable quanta. This information chunking provides a
104 mechanism for acquiring and expressing emotional repertoires which, without such
105 information compression, would be biologically unwieldy or difficult to implement. This

106 model has given rise to several postulates that have already been partially tested and
107 validated.

108 First, it suggests that, in functional terms, the STN is a constituent part of all the
109 distributed networks that subtend specific emotional subprocesses. This hypothesis was
110 confirmed in a high-resolution functional magnetic resonance imaging (fMRI) study of
111 healthy individuals (Péron, Frühholz, Ceravolo, & Grandjean, 2015) that explored the
112 structural and functional connectivity of the STN with other brain regions related to vocal
113 emotion, by combining diffusion tensor imaging and psychophysiological interaction analysis.

114 Second, it suggests that the basal ganglia, and more specifically the STN, are sensitive
115 to rhythm, owing to their intrinsic functional role of rhythm organizer, or coordinator of
116 neural patterns. In a more operational way, the model hypothesizes that the STN is involved
117 in i) all stages of emotion processing, and ii) all emotion processing irrespective of stimulus
118 valence (positive or negative) and sensory modality (e.g., visual or auditory). This has been
119 confirmed by intracranial local field potential recordings in patients with PD undergoing DBS
120 (Kühn *et al.*, 2005; Péron *et al.*, 2017).

121 Third and last, the model suggests that although STN DBS restores motor functions,
122 the surgery impairs nonmotor functions such as emotion processing. More specifically, STN
123 DBS restores the functional synchronization of the motor loop while at the same time
124 desynchronizing the limbic one (Péron *et al.*, 2013). The model further suggests that the
125 metabolic modifications correlating with emotional disturbances following surgery are both
126 task dependent and sensory input dependent (Péron *et al.*, 2013). This hypothesis has been
127 tested and validated for most emotional components, including the recognition of facial
128 emotions (Le Jeune *et al.*, 2008), the affective component of theory of mind (Péron, Le Jeune,
129 *et al.*, 2010), subjective emotional experiences or feelings (Ory *et al.*, 2015), and action

130 tendencies (Le Jeune et al., 2009). However, it has yet to be tested for the recognition of vocal
131 emotions (i.e., emotional prosody), defined as suprasegmental changes in the course of a
132 spoken utterance, encompassing intonation, amplitude, envelope, tempo, rhythm, and voice
133 quality (Grandjean, Banziger, & Scherer, 2006).

134 Finally, a recent study in the field of emotion recognition in PD indicated that the
135 asymmetry of motor symptoms is an important clinical factor, in that it may influence the
136 presence or severity of affective disorders in PD . In this study, results indicated that patients
137 with left-sided motor symptoms (LPD) displayed vocal emotion deficits. These correlated
138 with the asymmetry of these motor symptoms, as well as with glucose metabolism
139 modifications in the right brain network subtending higher-order processes of vocal emotion
140 recognition. This inferred differential impact of PD motor symptom asymmetry on the
141 recognition of emotional prosody was recently corroborated by a meta-analysis (Coundouris,
142 Adams, Grainger, & Henry, 2019). However, the interaction of this variable with the effects
143 of STN DBS has yet to be explored.

144

145 **1.1 Aim of the study**

146 In this context, the purpose of the present study was twofold. The *first aim* was to test
147 the notion that the STN is a functional component of the brain network subtending the
148 recognition of emotional prosody at the metabolic level. The *second aim* was to test the
149 impact of motor asymmetry on emotional performances before and after DBS. We therefore
150 combined and correlated the emotional prosody performances of 29 consecutive patients with
151 PD who underwent STN DBS in pre- versus postoperative conditions with modifications in
152 cerebral glucose metabolism, as assessed with 18-fluorodeoxyglucose positron emission
153 tomography (^{18}F FDG-PET), and according to the precise anatomical positions of the

154 stimulation contacts within the target structure. The patients were carefully selected to create
155 two clinically homogeneous subgroups of patients that could be differentiated by the
156 lateralization of their motor symptoms, as attested by the calculation of an asymmetry index.

157

158 **1.2 Predictions**

159 *Regarding behavioral results*, on the strength of previous results concerning the
160 effects of STN DBS on emotional prosody recognition in patients with PD (Péron, Cekic, et
161 al., 2015; Péron, Grandjean, et al., 2010), we expected to observe a significant modulation of
162 emotional prosody recognition scores in the postoperative condition, but no difference in the
163 preoperative condition between the PD group and a group of healthy controls (HC). Given the
164 results reported by Stirnimann et al. (2018), we predicted that these effects would be driven
165 by the LPD subgroup (i.e., patients with greater right hemispheric brain dysfunction).

166 *Regarding cognitive-metabolic results*, on the basis of Péron et al.'s model (2013), we
167 expected to find significant correlations between modifications in emotion recognition
168 performances in the postoperative condition and glucose metabolism modifications in the
169 brain network subtending emotional prosody recognition, namely the orbitofrontal and
170 auditory cortices (i.e., voice-sensitive areas), amygdala, basal ganglia (notably the striatum),
171 and posterior cerebellum (Ethofer, Anders, Erb, Droll, et al., 2006; Ethofer, Anders, Erb,
172 Herbert, et al., 2006; Ethofer et al., 2011; Frühholz, Ceravolo, & Grandjean, in press;
173 Grandjean et al., 2005; Sander et al., 2005; Schirmer & Kotz, 2006; Wildgruber, Ethofer,
174 Grandjean, & Kreifelts, 2009).

175

176 2 PARTICIPANTS AND METHODS

177 2.1 Participants

178 One group of patients with PD and one HC group took part in the study. All the
179 patients met the clinical criteria of the Parkinson's UK Brain Bank for idiopathic PD (Hughes,
180 Daniel, Kilford, & Lees, 1992).

181 2.1.1 Patients with Parkinson's disease (Table 1)

182 The patient group consisted of a series of 29 consecutive patients with medically
183 intractable PD who underwent bilateral STN DBS at Rennes University Hospital (France).
184 Standard selection and exclusion criteria for surgery were applied to all patients (Welter et al.,
185 2002). In particular, patients with brain atrophy were excluded on the basis of the
186 preoperative MRI. There were 16 men and 13 women in the patient group. Their mean age at
187 surgery was 56.5 years ($SD = 7.98$, range = 36-68), and their mean education level (in years
188 of school completed) was 11.30 ($SD = 3.60$, range = 6-20). According to the criteria of the
189 Edinburgh Handedness Inventory (Oldfield, 1971), 27 patients were right-handed, and two
190 were left-handed. Their mean disease duration at surgery was 11.20 years ($SD = 4.20$, range =
191 6-22). The total levodopa-equivalent daily dose (LEDD) was calculated on the basis of
192 Lozano et al. (1995): $M = 1280.76$ mg ($SD = 588.50$, range = 360-2520) before STN DBS and
193 $M = 717.21$ mg ($SD = 562.47$, range = 0-2020) after STN DBS.

194 The patients with PD were divided into two subgroups, based on side of symptom
195 onset: primarily left-affected (LPD; $n = 13$) versus primarily right-affected (RPD; $n = 16$). We
196 then calculated an asymmetry index based on the lateralized items (Items 20–26) of Part III of
197 the Unified Parkinson's Disease Rating Scale (UPDRS III; Fahn & Elton, 1987), by
198 subtracting the item scores related to the left side of the body from the item scores related to
199 the right side of the body, in order to use the patients' current asymmetry status to corroborate
200 our distinction. *T* tests for independent groups revealed a significant difference between the

201 two subgroups on the asymmetry index in both the on-dopa ($t = -4.72, p < .001$) and off-dopa
 202 ($t = -3.25, p = .003$) conditions. In the preoperative condition, the two patient subgroups were
 203 otherwise similar, in terms of sex ratio (8 women and 8 men in the RPD group; 6 women and
 204 7 men in the LPD group), age, education level, age at motor symptom onset, disease duration,
 205 and stage of the disease (Table 1).

206

207 **Table 1. Sociodemographic data before STN DBS for the two patient subgroups (RPD**
 208 **and LPD) ($n = 29$)**

	RPD group Mean \pm <i>SD</i>	LPD group Mean \pm <i>SD</i>	<i>T</i> value and <i>p</i> value
Age (years)	56.13 \pm 6.69	57.00 \pm 9.60	$t = -.29, p = .8$
Education level (years)	10.63 \pm 3.81	12.08 \pm 3.03	$t = -1.08, p = .3$
Age at motor symptom onset (years)	45.81 \pm 7.60	46.15 \pm 7.55	$t = -.12, p = .9$
Disease duration (years)	11.19 \pm 3.58	11.15 \pm 4.69	$t = .02, p = .9$
Levodopa-equivalent daily dose (LEDD)	1248.85 \pm 05.23	1306.69 \pm 93.50	$t = -.26, p = .8$

209 *Note.* *T* test for independent groups. *SD*: standard deviation; LPD: patients with PD exhibiting
 210 predominantly left-sided motor symptoms; RPD: patients with Parkinson's disease exhibiting
 211 predominantly right-sided motor symptoms.

212 **2.1.2 Matched healthy controls**

213 The HC group consisted of 29 healthy matched individuals who had no history of
 214 neurological disease, head injury or alcohol abuse, and displayed no signs of dementia, as
 215 attested by their scores on the Mattis Dementia Rating Scale (Mattis, 1988) (mean score =
 216 141.70, *SD* = 1.70). There were 16 men and 13 women in this group. Their mean age was
 217 54.35 years (*SD* = 8.50, range = 35-66), and their mean education level was 12.40 years (*SD* =

218 2.50, range = 9-15). According to the criteria of the Edinburgh Handedness Inventory
219 (Oldfield, 1971), 27 HC participants were right-handed and two were left-handed.

220 The two groups (whole PD vs. HC) were comparable for handedness and sex ratio.
221 Furthermore, there was no statistical difference between the two groups on either age ($t = -$
222 $1.274, p = .2$) or education level ($t = 1.594, p = .1$).

223 After receiving a full description of the study, all participants gave their written
224 informed consent, and the study was conducted in accordance with the Declaration of
225 Helsinki.

226 **2.2 General procedure**

227 All patients were assessed 3 months before and 3 months after surgery with motor,
228 PET, and neuropsychological tests. These evaluations were all performed in the same week.

229 All patients had stimulation turned on and were on levodopa when they underwent the PET
230 and neuropsychological assessments.

231 **2.3 Motor assessments**

232 All patients were evaluated according to the Core Assessment Program for
233 Intracerebral Transplantation (Langston et al., 1992) and scored on the UPDRS I-IV (Fahn &
234 Elton, 1987), Hoehn and Yahr scale (H&Y, Hoehn & Yahr, 1967), and Schwab and England
235 scale (S&E, Schwab & England, 1969) 3 months before and 3 months after surgery. Patients
236 were assessed on and off levodopa before and after surgery. Stimulation remained on after
237 surgery.

238 **2.4 Neurosurgery and electrode location (SI 1)**

239 Quadripolar (from 0 for the most ventral contact to 3 for the most dorsal) 3389 DBS
240 electrodes (Medtronic, Minneapolis, MN, USA) were implanted bilaterally in the STN in a
241 single operating session. The overall methodology was similar to that previously described by
242 Benabib and colleagues (2000). A brain MRI was performed at the onset of the surgical

243 procedure, to calculate the stereotactic coordinates for positioning the two selected electrode
244 contacts (one on the left and one on the right). The intended coordinates at the tip of Contact 0
245 were 10-12 mm from the midline, 0-3 mm behind the midcommissural point, and 3-5 mm
246 below the anterior commissure-posterior commissure line. During the operation, the final
247 course and depth of the electrodes was determined by the best effect obtained on rigidity with
248 no side effects and at the lowest voltage. A three-dimensional computed tomography brain
249 scan performed a few days later confirmed the position of the electrodes. The exact contact
250 locations for each patient and for each of the right and left electrodes are available in
251 Supplementary Material SI 1.

252 In all patients, chronic stimulation was monopolar, using a single contact of the
253 quadripolar electrode chosen for the best motor improvement. The stimulation characteristics
254 were as follows: mean pulse width 60 μ s for the right side ($SD = 0$) and 60 μ s ($SD = 0$) for the
255 left side, mean frequency 133 Hz ($SD = 8.2$) for the right side and 131 Hz ($SD = 6.1$) for the
256 left side, and mean voltage 2.2 V ($SD = 0.6$) for the right side and 2.2 V ($SD = 0.6$) for the left
257 side.

258 **2.5 Neuropsychological and psychiatric assessment**

259 A short neuropsychological and psychiatric battery was administered to participants
260 prior to the vocal emotion recognition sessions (Péron et al., 2011; Péron, Grandjean, et al.,
261 2010). This battery included the MDRS (Mattis, 1988) and a series of tests to assess frontal
262 executive functions: Nelson modified Wisconsin Card Sorting Test (MCST, Nelson, 1976),
263 Trail Making Test (TMT, Reitan, 1958), Categorical and Literal Fluency Test (Cardebat,
264 Doyon, Puel, Goulet, & Joannette, 1990), Action (Verb) Fluency Task (Woods et al., 2005),
265 and Stroop test (Stroop, 1935). Depression was assessed with the Montgomery-Åsberg
266 Depression Rating Scale (MADRS, Montgomery & Asberg, 1979). This scale was chosen
267 because of the predominance of psychic items over somatic ones, thus limiting interference

268 with the PD symptoms. Finally, the State-Trait Anxiety Inventory (STAI, Spielberger,
269 Gorsuch, Lushene, Vagg, & Jacobs, 1993) was used to assess anxiety, and the Apathy
270 Evaluation Scale (clinician version; (Marin, Biedrzycki, & Firinciogullari, 1991) to assess
271 apathy.

272

273 **2.6 Vocal emotion recognition assessment**

274 **2.6.1 Stimuli**

275 All participants were exposed to a set of vocal stimuli (Péron *et al.*, 2011; Péron,
276 Grandjean, *et al.*, 2010). These stimuli, extracted from the database developed and validated
277 by Banse and Scherer (1996), consisted of short segments of meaningless speech
278 (pseudoword 1: fi goet laiʃ ʃã kil gɔs tɛr, pseudo-word 2: h'et s'õdik pr'õg nj'y v'entzi),
279 obtained by concatenating different syllables found in Indo-European languages so that they
280 would be perceived of as natural utterances, with emotional intonation (across different
281 cultures) but no semantic content. Four categories of emotional prosody (anger, fear,
282 happiness, and sadness), together with a neutral condition, were used in the present study. We
283 selected utterances produced by 12 different actors (6 women and 6 men), each expressed
284 with five different prosodies (anger, fear, happiness, neutral, and sadness). The set of vocal
285 stimuli (pseudowords) comprised 60 stimuli (12 actors \times 5 emotion conditions) and is
286 extensively described elsewhere (Péron, Cekic, *et al.*, 2015; Péron, Grandjean, *et al.*, 2010).

287 **2.6.2 Vocal emotion recognition procedure**

288 All stimuli were presented bilaterally via stereo headphones with an Authorware
289 program designed especially for this study. Participants sat comfortably in a quiet room in
290 front of the computer and looked at a fixation cross while listening to the stimuli. They were
291 told that they would hear meaningless speech uttered by male/female actors and that these
292 actors would express emotions through their utterances. Participants were required to listen to

293 each stimulus, after which they were asked to rate its emotional content on a set of visual
294 analogue scales ranging from *Not at all* to *Very much*, which were simultaneously displayed
295 on the computer screen (see Appendix). More specifically, participants rated each stimulus on
296 six scales: one scale for each featured emotion (anger, fear, happiness, and sadness), one for
297 neutral, and one for the *surprise* emotion, so that we could determine whether the fear
298 emotion expressed by the human voice was confused with surprise, as is the case with facial
299 expressions (Ekman, 2003; Scherer & Ellgring, 2007). Participants were told that they could
300 listen again to each stimulus as many as six times, by clicking on a button on the computer
301 interface (click counter). Participants were given two examples to familiarize themselves with
302 the task.

303 **2.6.3 Audiometric screening procedure**

304 To ensure that all participants had normal hearing, we carried out a standard
305 audiometric screening procedure (AT-II-B audiometric test) to measure tonal and vocal
306 sensitivity. This was done in the Ear, Nose and Throat Department of Rennes University
307 Hospital. None of the patients included in the study wore hearing aids or had a history of
308 tinnitus or a hearing impairment.

309 As described elsewhere (Le Jeune *et al.*, 2008; Péron, Biseul, *et al.*, 2010; Péron,
310 Grandjean, *et al.*, 2010; Péron *et al.*, 2009), Versions A and B of the emotional recognition
311 task were counterbalanced, to avoid a list effect between the pre- and postoperative conditions
312 in the PD group. The protocol was completed in a single 90-minute session.

313 **2.7 PET imaging**

314 **2.7.1 Acquisition**

315 All patients underwent the ^{18}F FDG-PET scans in a resting state with their eyes open.
316 They underwent two scans while on their antiparkinsonian medication: the first was
317 performed 3 months before surgery, and the second 3 months after surgery, with the

318 stimulator switched on. PET measurements were performed with a dedicated Discovery ST
319 PET scanner (GEMS, Milwaukee, WI, USA) in 2D mode with an axial field of view of 15.2
320 cm. A 222-296 MBq injection of ^{18}F FDG was administered intravenously under standardized
321 conditions (in a quiet, dimly lit room with the patient's eyes and ears open), with normal
322 fasting blood glucose < 1.4 g/l before injection. During acquisition, the patient's head was
323 immobilized with a head holder. A cross-laser system was used to achieve stable and
324 reproducible positioning. A 20-minute 2D emission scan was performed 30 minutes post-
325 injection and after X-ray-based attenuation correction. The patient was positioned at the
326 center of the field of view. Following scatter, dead time, and random corrections, the PET
327 images were reconstructed by 2D filtered back projection, yielding 47 contiguous transaxial
328 3.75-mm thick slices.

329 ***2.7.2 PET image transformation***

330 Using a method described elsewhere (Le Jeune *et al.*, 2008), we analyzed the data with
331 statistical parametric mapping (SPM) software (Wellcome Department of Cognitive
332 Neurology, London, UK) implemented in MATLAB Version 8 (Mathworks Inc., Sherborn,
333 MA, USA). All the patients' images were first realigned and normalized to MNI space.

334 **2.8 Statistical analysis**

335 ***2.8.1 Analyses testing predictions about behavioral results***

336 ***Sociodemographic, neuropsychological, and psychiatric data.*** Intergroup
337 comparisons were performed using t tests for two independent groups. Intragroup
338 comparisons were performed using t tests for two dependent groups, to evaluate the effect of
339 experimental condition.

340 ***Vocal emotion recognition data.*** We calculated three generalized linear mixed models
341 (GLMMs) with participant as the random factor. This type of statistical model allows random
342 effects such as interindividual variability to be controlled, in addition to fixed effects. Using R

343 software, we calculated a first GLMM with three within-participants factors: emotion (five
344 levels), scale (six levels), and condition (pre- vs. postoperative; two levels). A second GLMM
345 was run with emotion (five levels) and scale (six levels) as within-participants factors, and
346 group (PD preoperative vs. HC; two levels) as a between-participants factor. A third GLMM
347 was calculated with emotion (five levels) and scale (six levels) as within-participants factors,
348 and group (PD postoperative vs. HC; two levels) as a between-participants factor. To
349 investigate the effects in greater detail, for each model, we used the phia package in R and
350 performed contrasts between the groups (or conditions) for each prosodic category and each
351 rating scale. **Each p value yielded by the contrasts was false discovery rate (FDR)**
352 **corrected.**

353 *Relationship between vocal emotion recognition performances and secondary*
354 *variables.* To assess the relationships between the psychiatric, clinical, neuropsychological
355 and sociodemographic variables and the recognition of emotional prosody variables, we
356 entered these variables in multiple regression models. More specifically, the postoperative -
357 preoperative deltas for emotional prosody ratings were entered as dependent variables and the
358 postoperative - preoperative deltas for the sociodemographic, psychiatric, clinical, and
359 neuropsychological variables, as well as the contact locations, were entered as independent
360 variables. In addition, relative to our operational hypotheses, we included the preoperative on-
361 dopa motor asymmetry index. The regression analyses were performed with experimental
362 emotional conditions and secondary variables of interest (i.e., those reported to be significant
363 between the pre- and postoperative conditions), in order to avoid Type I errors. The results of
364 forward, backward, and stepwise regressions were all consistent.

365 *2.8.2 Analyses testing predictions about cognitive-metabolic results*

366 The SPM software established correlations between pre- versus postoperative changes
367 in recognition of emotional prosody data and pre- versus postoperative changes in brain FDG

368 uptake. To identify those regions that correlated significantly with the recognition of
369 emotional prosody, we tested a general linear “single subject, covariates only” model for
370 every voxel, with emotional prosody as a covariant: one model for each of the emotional
371 prosody recognition-dependent variables that were found to be significantly different in the
372 postoperative condition compared with the preoperative one, between the RPD and LPD
373 subgroups, or between the PD patient group and HC. As levodopa medication can influence
374 neural metabolism, we included LEDD as a nuisance variable. Relative to our operational
375 hypotheses, and as with the cognitive-emotional regressions, we included the preoperative on-
376 dopa motor asymmetry index as a second nuisance variable. This yielded a regression
377 coefficient that was then converted into a t value. Two t tests were performed, one intended to
378 reveal correlations between modifications in emotional scores and decreased cerebral glucose
379 metabolism, the other to reveal correlations between these modifications and increased
380 cerebral FDG uptake. Next, t statistic parametric maps were calculated for each covariate.
381 Clusters of a minimum of 70 contiguous voxels with a threshold of $p < 0.001$ (corrected for
382 multiple comparisons) were deemed to be significant for cortical structures, while clusters of
383 a minimum of 25 contiguous voxels with a threshold of $p < 0.001$ (corrected for multiple
384 comparisons) were deemed to be significant for smaller structures such as the basal ganglia,
385 thalamus and amygdala, as well as for cerebellar structures.

386

387 **3 RESULTS**

388 **3.1 Clinical and motor results (Table 2)**

389 **3.1.1 Intergroup comparisons**

390 Apart from the motor asymmetry index (see Methods), no significant difference
391 between the LPD and RPD patients was observed in either the pre- or postoperative condition
392 (all p s > .08).

393 **3.1.2 Intragroup comparisons**

394 For both patient subgroups, we observed a significant motor improvement 3 months
395 after surgery. For the RPD subgroup, the effects were significant for the motor UPDRS III
396 score in both the off-dopa ($t = 4.79, p < .001$) and on-dopa ($t = 4.16, p = .008$) conditions, the
397 off-dopa S&E score ($t = 2.08, p = .046$), and the off-dopa H&Y score ($t = -2.18, p = .04$). For
398 the LPD subgroup, the effects were only significant for the motor UPDRS III score in the off-
399 dopa condition ($t = 4.1, p = .001$). LEDD decreased significantly after surgery for both
400 subgroups (RPD: $t = -3.41, p < .001$; LPD: $t = -2.09, p = .047$). All the data, other effects, p
401 and statistical values are available in full in Table 2.

402

403

404 **Table 2. Motor scores before (preoperative condition, baseline) and after (postoperative**
 405 **condition, M+3) STN DBS for patients with PD ($n = 29$), according to subgroup (LPD or**
 406 **RPD).**

	RPD Off-dopa		RPD On-dopa		LPD Off-dopa		LPD On-dopa	
	Pre Mean \pm SD	Post Mean \pm SD	Pre Mean \pm SD	Post Mean \pm SD	Pre Mean \pm SD	Post Mean \pm SD	Pre Mean \pm SD	Post Mean \pm SD
UPDRS III	35.34 \pm 15.87	14.83 \pm 8.38**	8.16 \pm 5.32	4.90 \pm 3.66*	31.12 \pm 9.01	15.46 \pm 9.98*	8.27 \pm 6.39	4.81 \pm 3.82
S&E (%)	56.54 \pm 23.00	74.38 \pm 23.00**	81.43 \pm 24.13	93.75 \pm 6.19	70.77 \pm 15.49	76.92 \pm 15.49	87.69 \pm 12.56	94.62 \pm 10.32
H&Y	2.60 \pm 1.05	1.72 \pm 1.17*	1.1 \pm 0.99	0.91 \pm 1.07	2.19 \pm 0.75	2.04 \pm 0.77	1.03 \pm 0.83	0.81 \pm 0.99
LEDD	NA	NA	1306.69 \pm 593.18	685.47 \pm 544.12**	NA	NA	1248.75 \pm 605.23	753.85 \pm 603.07*

407
 408 *Note.* *T* test for dependent groups. STN DBS: subthalamic nucleus deep brain stimulation;
 409 LPD: patients with Parkinson's disease exhibiting predominantly left-sided motor symptoms;
 410 RPD: patients with Parkinson's disease exhibiting predominantly right-sided motor
 411 symptoms; UPDRS: Unified Parkinson's Disease Rating Scale; *SD*: standard deviation; S&E:
 412 Schwab & England scale; H&Y: Hoehn & Yahr scale; LEDD: levodopa-equivalent daily
 413 dose; NA: not applicable. * $p < 0.05$. ** $p < 0.001$.

414

415 3.2 Neuropsychological background and psychiatric results (Table 3)

416 3.2.1 Intergroup comparisons

417 *RPD versus HC.* In the preoperative condition, there were significant differences
 418 between the RPD and HC groups on the TMT B-A ($t = -2.92$, $p = .01$), the numbers of criteria
 419 ($t = 2.49$, $p = .02$) and errors ($t = -2.56$, $p = .01$) in the MCST, the Action (Verb) Fluency Task
 420 ($t = -2.13$, $p = .04$), MADRS ($t = -3.95$, $p < .01$), and STAI A ($t = -2.13$, $p = .04$). In the

421 postoperative condition, there were significant differences between the RPD and HC groups
422 on the TMT B-A ($t = -2.99, p = .01$) and MDRS ($t = -2.8, p = .01$). The RPD subgroup
423 therefore had poorer cognitive performances than HC and were more depressed.

424 *LPD versus HC.* In the preoperative condition, no significant differences were found
425 for neuropsychological background and psychiatric tests. In the postoperative condition
426 however, there were significant differences on the number of criteria ($t = 2.15, p = .04$) in the
427 MCST and on the Action (Verb) Fluency Task ($t = 2.19, p = .03$). The LPD subgroup
428 therefore had poorer cognitive performances than HC.

429 *LPD versus RPD.* Interestingly, the RPD and LPD subgroups differed significantly in
430 the preoperative condition on STAI A ($t = 2.69, p = .01$) and B ($t = 2.17, p = .01$), with RPD
431 patients scoring higher on anxiety than LPD patients. In the postoperative condition, no
432 significant difference was found between the RPD and LPD subgroups on any of the
433 neuropsychological background or psychiatric tests.

434 **3.2.2 Intragroup comparisons**

435 *Within RPD.* No significant difference was found between the pre- and postoperative
436 conditions for neuropsychological background and psychiatric tests, except for phonemic
437 verbal fluency ($t = -3.19, p = .009$), on which RPD patients performed more poorly in the
438 postoperative condition than in the preoperative one.

439 *Within LPD.* No significant difference was found between the preoperative and
440 postoperative conditions for neuropsychological background and psychiatric tests, except for
441 phonemic verbal fluency ($t = -3.05, p = .01$) and the MDRS ($t = -2.53, p = .03$), on which
442 LPD patients performed more poorly in the postoperative condition than in the preoperative
443 one.

444 **Table 3. Performances of patients with PD before (preoperative condition, M-3, $n = 29$)**
 445 **and after (postoperative condition, M+3, $n = 29$) STN DBS, according to subgroup (LPD**
 446 **or RPD), and HC ($n = 29$) on neuropsychological tests**

	RPD Preoperative Mean \pm SD	RPD Postoperative Mean \pm SD	LPD Preoperative Mean \pm SD	LPD Postoperative Mean \pm SD	HC Mean \pm SD
MDRS (/144)	140.31 \pm 2.94	141.00 \pm 2.22	140.92 \pm 1.89	138.08 \pm 4.36 [#]	141.68 \pm 1.70
Stroop Test - Interference	1.73 \pm 8.17	2.48 \pm 7.55	3.60 \pm 6.39	5.21 \pm 7.52	3.09 \pm 6.83
TMT B-A (s)	75.06 \pm 47.08 [*]	95.93 \pm 84.64 [*]	64.54 \pm 79.16	75.69 \pm 76.2	42.56 \pm 23.87
Categorical verbal fluency (2 min)	30.38 \pm 9.49	28.94 \pm 9.24	27.69 \pm 13.30	29.38 \pm 12.37	32.64 \pm 7.52
Phonemic verbal fluency (2 min)	22.69 \pm 6.07	19.63 \pm 5.29 [#]	20.92 \pm 7.43	17.00 \pm 6.38 [#]	20.96 \pm 6.29
Action (Verb) Fluency (1 min)	13.06 \pm 6.21 [*]	13.56 \pm 5.12	14.38 \pm 6.59	13.31 \pm 5.95 [*]	16.24 \pm 4.85
MCST - Number of categories (/6)	5.54 \pm 0.82 [*]	5.82 \pm 0.35	5.75 \pm 0.62	5.21 \pm 1.75 [*]	5.96 \pm 0.20
MCST - Number of errors	5.50 \pm 4.56 [*]	3.63 \pm 3.59	3.58 \pm 4.68	4.67 \pm 6.84	2.80 \pm 2.10
MCST - Number of perseverative errors	1.44 \pm 1.82	1.13 \pm 1.67	1.08 \pm 2.07	1.83 \pm 3.33	0.56 \pm 0.77
MADRS	5.60 \pm 4.39 [*]	4.73 \pm 4.61 [*]	3.15 \pm 3.48	3.38 \pm 4.46	1.29 \pm 2.07
STAI-A State	40.62 \pm 11.84 [*]	34.54 \pm 7.78	29.64 \pm 5.37 [@]	32.36 \pm 11.25	31.06 \pm 10.70
STAI-B Trait	44.79 \pm 8.62	41.86 \pm 9.87	36.64 \pm 11.20 [@]	38.64 \pm 11.25	39.82 \pm 9.16
AES Total	32.40 \pm 5.45	34.73 \pm 9.66	30.08 \pm 7.54	30.69 \pm 7.06	-

447 *Note.* STN DBS: subthalamic nucleus deep brain stimulation; LPD: patients with Parkinson's
 448 disease exhibiting predominantly left-sided motor symptoms; RPD: patients with Parkinson's
 449 disease exhibiting predominantly right-sided motor symptoms; HC: healthy controls; MDRS:
 450 Mattis Dementia Rating Scale; TMT: Trail Making Test; MCST: Modified Wisconsin Card
 451 Sorting Test; MADRS: Montgomery-Åsberg Depression Rating Scale; STAI: State-Trait
 452 Anxiety Inventory; AES, Apathy Evaluation Scale; *SD*: standard deviation. ^{*} $p < 0.05$
 453 compared with HC group (t test for independent samples). [#] $p < 0.05$ compared with
 454 preoperative condition (t test for dependent samples). [@] $p < 0.05$ compared with RPD group (t
 455 test for independent samples).

456

457 **3.3 Vocal emotion recognition results (Tables 4 & 5)**

458 Interestingly, analysis revealed the following significant interaction effects: Emotion ×
459 Scale × Condition × Side of symptom onset, $F(20, 20733) = 1.8, p = .01$; Emotion × Scale ×
460 Side of symptom onset, $F(20, 20733) = 4.4, p < .001$; Scale × Condition × Side of symptom
461 onset, $F(5, 20733) = 5.28, p < .001$; Condition × Emotion × Scale, $F(20, 20733) = 2.1, p <$
462 $.001$; Emotion × Scale, $F(20, 20733) = 376.44, p < 0.001$; Scale × Side of symptom onset,
463 $F(20, 20733) = 8.42, p < .001$; and Scale × Condition, $F(5, 20733) = 3.76, p = .002$. There
464 were also main effects of emotion, $F(4, 20733) = 13.67, p < .001$, and scale, $F(5, 20733) =$
465 $37.1, p < .001$. There was no significant effect of either Condition × Emotion × Side of
466 symptom onset, $F < 1$, Emotion × Side of symptom onset, $F < 1$, Emotion × Condition, $F < 1$,
467 or Condition × Side of symptom onset, $F(4, 20733) = 2.43, p = .12$. Nor was there a
468 significant main effect of either condition, $F(1, 20733) = 3.25, p = .07$, or side of symptom
469 onset, $F < 1$.

470 To investigate these effects in greater detail, we ran Condition × Side of symptom
471 onset × Scale interaction analyses for each separate emotion. Contrasts (FDR corrected) were
472 then performed between the groups for each prosodic category and ratings on (a) the target
473 scale, that is, the scale (e.g., Anger) corresponding to the stimulus emotion (e.g., anger), and
474 (b) the nontarget scales, that is, the scales that did not correspond to the stimulus emotion (e.g.
475 Fear scale for anger stimulus). Contrasts were performed for the nontarget scales in order to
476 investigate the patterns of confusion between the different emotions. Means and standard
477 deviations are available in Table 4, and summarized results in Table 5.

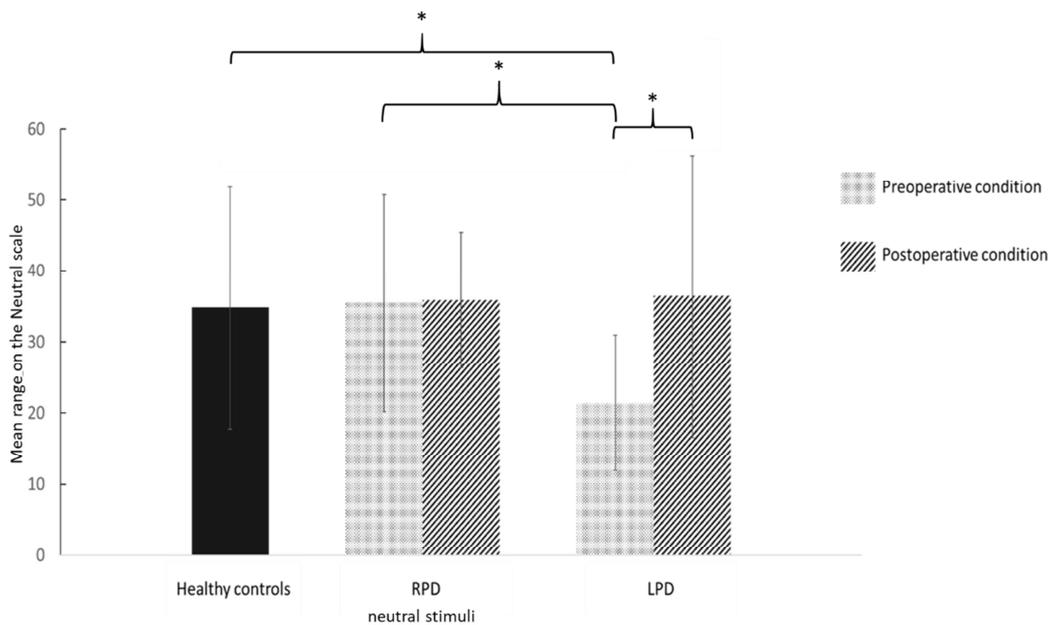
478 In the preoperative condition, compared with both the RPD subgroup and HC, the
479 LPD subgroup exhibited emotional deficits for ratings on the target scales when they listened
480 to neutral (Fig. 1) and happiness stimuli. Moreover, compared with HC, the LPD subgroup

481 exhibited emotional deficits for ratings on the target scale when they listened to sadness
482 stimuli. These significant differences were no longer present in the postoperative condition.

483

484 **Figure 1. Mean ratings (and standard deviations) across all three groups (RPD,**
485 **LPD and HC) on the Neutral scale when the stimulus was neutral**

486



487

488

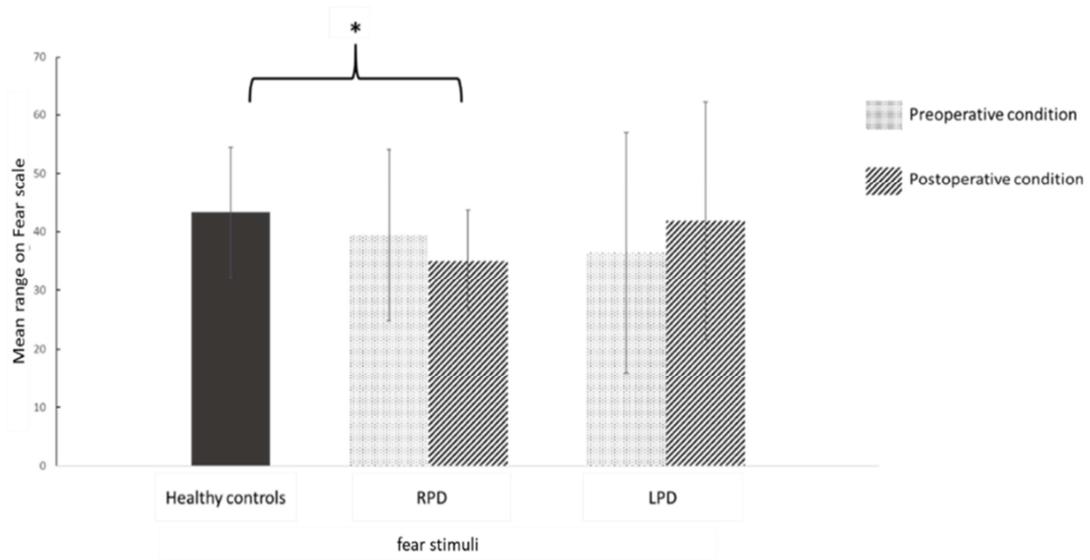
489 By contrast, for ratings on the Fear scale when participants listened to fear stimuli, the
490 RPD subgroup did not differ significantly from either the HC or LPD in the preoperative
491 condition. However, they provided a significantly higher number of emotional misattributions
492 in the postoperative condition, compared with HC (Fig. 2).

493

494

495 **Figure 2. Mean ratings (and standard deviations) for all three groups (RPD, LPD and**
496 **HC) on the Fear scale when the stimulus was fear.**

497



498

499 All the effects are summarized in Table 5.

500

501

502 **Table 4. Mean ratings (standard deviations) of pseudoword stimuli in emotional prosody**
 503 **task for patients with PD (preoperative vs. postoperative condition), according to**
 504 **subgroup (LPD; $n = 13$ vs. RPD; $n = 16$), and for HC**

<i>RPD Preoperative condition (baseline) (n = 16)</i>						
Emotion	Anger scale	Happiness scale	Neutral scale	Fear scale	Surprise scale	Sadness scale
Anger	46.20 (\pm 11.91)	1.76 (\pm 2.50)	5.03 (\pm 5.88)	4.57 (\pm 5.27)	7.72 (\pm 6.66)	0.66 (\pm 1.97)
Fear	7.34 (\pm 7.26)	3.16 (\pm 2.58)	4.23 (\pm 3.83)	38.61 (\pm 14.65)	8.68 (\pm 10.29)	10.03 (\pm 12.94)
Happiness	5.36 (\pm 4.92)	34.07 (\pm 11.99)	1.77 (\pm 3.06)	6.95 (\pm 6.73)	13.81 (\pm 10.57)	5.87 (\pm 6.19)
Neutral	0.15 (\pm 0.08)	6.41 (\pm 5.90)	34.40 (\pm 18.54)	0.67 (\pm 0.97)*	11.36 (\pm 8.32)	1.34 (\pm 1.69)
Sadness	0.98 (\pm 2.17)	1.06 (\pm 2.75)	18.93 (\pm 10.42)	8.91 (\pm 8.13)	3.52 (\pm 5.42)	33.58 (\pm 17.96)
<i>RPD Postoperative condition (M+3) (n = 16)</i>						
Emotion	Anger scale	Happiness scale	Neutral scale	Fear scale	Surprise scale	Sadness scale
Anger	48.39 (\pm 11.98)	0.71 (\pm 1.46)	6.51 (\pm 6.72)	5.18 (\pm 7.11)	9.08 (\pm 6.34)	1.13 (\pm 1.81)
Fear	6.74 (\pm 5.34)	3.38 (\pm 3.41)	5.67 (\pm 7.20)	34.88 (\pm 13.30)*	12.99 (\pm 9.91)	9.47 (\pm 8.48)
Happiness	3.85 (\pm 4.59)	30.45 (\pm 13.93)	4.61 (\pm 6.47)	6.12 (\pm 6.09)	19.70 (\pm 10.11)	6.50 (\pm 8.26)
Neutral	0.43 (\pm 0.54)	6.67 (\pm 6.60)	36.04 (\pm 15.29)	1.68 (\pm 1.83)*	11.83 (\pm 9.75)	1.63 (\pm 2.01)
Sadness	2.65 (\pm 4.08)	1.17 (\pm 2.20)	14.34 (\pm 12.09)	9.33 (\pm 7.44)	4.65 (\pm 5.87)	36.14 (\pm 17.23)
<i>LPD Preoperative condition (baseline) (n = 13)</i>						
Emotion	Anger scale	Happiness scale	Neutral scale	Fear scale	Surprise scale	Sadness scale
Anger	46.01 (\pm 13.67)	1.92 (\pm 4.95)	5.75 (\pm 3.97)	6.62 (\pm 11.14)	11.91 (\pm 10.91)	6.05 (\pm 12.14)
Fear	11.33 (\pm 14.70)	3.42 (\pm 7.14)	5.76 (\pm 7.51)	37.46 (\pm 21.02)	14.68 (\pm 12.56)	14.35 (\pm 15.37)
Happiness	9.39 (\pm 11.67)	23.29 (\pm 10.27)* [®]	2.52 (\pm 4.02)	10.41 (\pm 10.71)	24.03 (\pm 14.46) [®]	12.39 (\pm 12.12)
Neutral	5.69 (\pm 11.61)	7.22 (\pm 8.80)	22.67 (\pm 8.71)	4.94 (\pm 10.34)* [®]	17.69 (\pm 14.25) [®]	7.03 (\pm 12.44)
Sadness	5.07 (\pm 11.53)	2.01 (\pm 4.85)	19.12 (\pm 8.52)	11.94 (\pm 11.40)	6.82 (\pm 13.99)	30.65 (\pm 10.96)*
<i>LPD Postoperative condition (M+3) (n = 13)</i>						
Emotion	Anger scale	Happiness scale	Neutral scale	Fear scale	Surprise scale	Sadness scale
Anger	48.31 (\pm 13.51)	3.56 (\pm 10.13)	9.34 (\pm 10.71)	6.68 (\pm 11.11)	12.86 (\pm 12.72)	4.36 (\pm 12.31)
Fear	7.95 (\pm 11.37)	4.21 (\pm 12.32)	8.78 (\pm 11.98)	38.93 (\pm 17.64)	14.15 (\pm 14.57)	12.08 (\pm 11.06)
Happiness	8.66 (\pm 11.73)	24.66 (\pm 11.88)	7.73 (\pm 12.24)	14.06 (\pm 12.74)	19.83 (\pm 15.13)	13.29 (\pm 12.07)
Neutral	3.77 (\pm 11.56)	4.97 (\pm 8.81)	38.95 (\pm 18.24) [#]	3.93 (\pm 10.72)	18.61 (\pm 14.66) [®]	5.64 (\pm 13.03)
Sadness	4.13 (\pm 11.32)	3.41 (\pm 9.85)	21.14 (\pm 12.61)	9.11 (\pm 10.54)	5.6 (\pm 12.2)	36.58 (\pm 9.19)

HC group (n = 29)						
Emotion	Anger scale	Happiness scale	Neutral scale	Fear scale	Surprise scale	Sadness scale
Anger	51.97 (± 10.09)	1.29 (± 4.55)	4.22 (± 5.55)	6.40 (± 8.04)	11.26 (± 9.51)	2.24 (± 4.26)
Fear	8.75 (± 9.63)	1.27 (± 2.23)	2.67 (± 4.86)	43.46 (± 11.09)	12.04 (± 9.93)	14.56 (± 11.19)
Happiness	9.49 (± 7.41)	30.83 (± 10.23)	1.88 (± 3.26)	7.38 (± 4.62)	19.44 (± 10.81)	8.74 (± 7.12)
Neutral	1.09 (± 2.70)	6.76 (± 7.83)	34.57 (± 17.33)	1.20 (± 1.57)	16.34 (± 10.08)	3.23 (± 3.82)
Sadness	2.38 (± 4.26)	1.28 (± 2.38)	20.16 (± 13.86)	9.55 (± 7.17)	3.17 (± 3.95)	39.53 (± 16.96)

505

506 *Note.* PD: Parkinson's disease; *SD*: standard deviation; LPD: patients with Parkinson's
507 disease exhibiting predominantly left-sided motor symptoms; RPD: patients with Parkinson's
508 disease exhibiting predominantly right-sided motor symptoms; HC: healthy controls. * $p < .05$
509 compared with HC group (intergroup comparisons). # $p < 0.05$ compared with preoperative
510 condition (intragroup comparisons). @ $p < 0.05$ compared with RPD group (intergroup
511 comparisons).

512

513 **Table 5. Table summarizing vocal emotion recognition results (FDR corrected)**

Emotion	Scale	Intergroup comparisons		Intragroup comparisons (Pre vs. post)
		<i>Preoperative condition</i>	<i>Postoperative condition</i>	
Anger	Anger	<i>ns</i>	<i>ns</i>	<i>ns</i>
	Fear	<i>ns</i>	<i>ns</i>	<i>ns</i>
	Happiness	<i>ns</i>	<i>ns</i>	<i>ns</i>
	Neutral	<i>ns</i>	<i>ns</i>	<i>ns</i>
	Sadness	<i>ns</i>	<i>ns</i>	<i>ns</i>
	Surprise	<i>ns</i>	<i>ns</i>	<i>ns</i>
Fear	Anger	<i>ns</i>	<i>ns</i>	<i>ns</i>
	Fear	<i>ns</i>	RPD < HC	<i>ns</i>
	Happiness	<i>ns</i>	<i>ns</i>	<i>ns</i>
	Neutral	<i>ns</i>	<i>ns</i>	<i>ns</i>
	Sadness	<i>ns</i>	<i>ns</i>	<i>ns</i>
	Surprise	<i>ns</i>	<i>ns</i>	<i>ns</i>
Happiness	Anger	<i>ns</i>	<i>ns</i>	<i>ns</i>
	Fear	<i>ns</i>	<i>ns</i>	<i>ns</i>
	Happiness	LPD < RPD; LPD < HC	<i>ns</i>	<i>ns</i>
	Neutral	<i>ns</i>	<i>ns</i>	<i>ns</i>
	Sadness	<i>ns</i>	<i>ns</i>	<i>ns</i>
	Surprise	LPD > RPD	<i>ns</i>	<i>ns</i>
Neutral	Anger	<i>ns</i>	<i>ns</i>	<i>ns</i>
	Fear	<i>ns</i>	<i>ns</i>	<i>ns</i>
	Happiness	<i>ns</i>	<i>ns</i>	<i>ns</i>
	Neutral	LPD < RPD; LPD < HC	<i>ns</i>	LPD pre < LPD post
	Sadness	<i>ns</i>	<i>ns</i>	<i>ns</i>
	Surprise	LPD > RPD; RPD < HC	LPD < RPD ; RPD < HC	<i>ns</i>
Sadness	Anger	<i>ns</i>	<i>ns</i>	<i>ns</i>
	Fear	<i>ns</i>	<i>ns</i>	<i>ns</i>
	Happiness	<i>ns</i>	<i>s</i>	<i>ns</i>
	Neutral	<i>ns</i>	<i>ns</i>	<i>ns</i>
	Sadness	LPD < HC	<i>ns</i>	<i>ns</i>
	Surprise	<i>ns</i>	<i>ns</i>	<i>ns</i>

514

515 *Note.* LPD: patients with Parkinson's disease exhibiting predominantly left-sided motor
516 symptoms; RPD: patients with Parkinson's disease exhibiting predominantly right-sided
517 motor symptoms; HC: healthy controls; pre: preoperative condition; post: postoperative
518 condition; *ns*: Not statistically significant.

519

520 **3.4 Relationships between vocal emotion recognition performances and secondary**
521 **variables**

522 When the stimuli were neutral and the scale was Neutral, the best fit was achieved
523 using LEDD ($R^2 = .29, p = .008$).

524 When the stimuli were neutral and the scale was Surprise, the best fit was achieved
525 using the on-dopa off-stim UPDRS III score ($R^2 = .27, p = .007$) and x coordinate of the right
526 DBS electrode ($R^2 = .22, p = .005$).

527 When the stimuli were happiness and the scale Happiness, the best fit was achieved
528 using the y coordinate of the right DBS electrode ($R^2 = .12, p = .048$), x coordinate of the left
529 DBS electrode ($R^2 = .08, p = .02$), preoperative on-dopa motor asymmetry index ($R^2 = .08, p =$
530 $.003$), and Action (Verb) Fluency Task score ($R^2 = .03, p = .02$).

531 When the stimuli were happiness and the scale was Surprise, the best fit was achieved
532 using the on-dopa off-stim UPDRS III score ($R^2 = .22, p = .02$), off-dopa on-stim UPDRS III
533 score ($R^2 = .16, p = .03$), and Action (Verb) Fluency Task score ($R^2 = .09, p = .04$).

534 When the stimuli were fear and the scale was Fear, the best fit was achieved using the
535 MDRS score ($R^2 = .22, p = .02$), on-dopa S&E score ($R^2 = .22, p = .008$), x coordinate of the
536 right DBS electrode ($R^2 = .11, p = .04$), on-dopa off-stim UPDRS III score ($R^2 = .03, p = .02$),
537 number of categories in the MCST ($R^2 = .06, p = .02$), and Action (Verb) Fluency Task score
538 ($R^2 = .03, p = .02$).

539 When the stimuli were sadness and the scale Sadness, no significant results were
540 observed.

541

542

543 **Table 6. Regions with decreased or increased glucose metabolism following STN DBS in**
 544 **the patient group ($n = 29$), for each significant result**

Emotion / Scale	Regions	MNI X coordinates	MNI Y coordinates	MNI z coordinates	z value	Voxel number
<i>neutral / Neutral</i>	<i>Negative correlations:</i> Right cerebrum, frontal lobe, middle frontal gyrus (BA 6)	36	6	54	3.75	91
	<i>Positive correlations:</i> Right cerebellum, posterior lobe, Lobules VIII and VIIb	36	-44	-50	3.61	29*
<i>sadness / Sadness</i>	<i>Negative correlations:</i> Right temporal lobe, superior temporal gyrus (BA 41)	54	-24	6	3.90	167
	Right frontal lobe, inferior frontal gyrus (BA 45)	40	20	16	3.76	108
<i>happiness / Happiness</i>	<i>Positive correlations:</i> Right temporal lobe, superior temporal gyrus, insula (BA 38)	44	8	-16	3.58	30*
<i>fear / Fear</i>	<i>Negative correlations:</i> Left limbic lobe, parahippocampal gyrus (BA 35)	-16	-10	-24	3.82	29*
	Right cerebellum, anterior lobe of cerebellum, culmen, Lobules IV and V	26	-34	-26	3.79	36*

545 *Note.* Results for each emotion/Scale are ordered according to z score values. MNI: Montreal

546 Neurological Institute; BA: Brodmann area. $p < .001$ corrected. $k > 70$ for cortical structures.

547 $k > 25^*$ for subcortical and cerebellar structures.

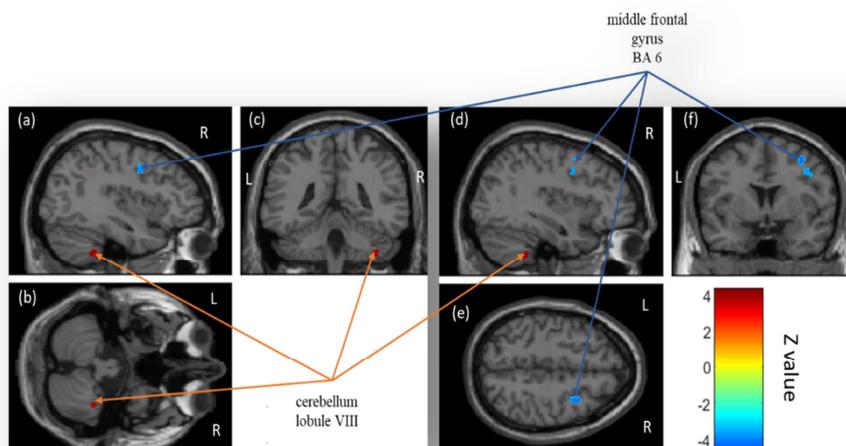
548 **3.5 Relationship between recognition of emotional prosody and cerebral metabolic**
 549 **results (Table 6 and Figs 3-6)**

550 **3.5.1 Model 1: Ratings on Neutral scale for neutral stimuli (Fig. 3)**

551 Correlations between decreased cerebral glucose metabolism and increased ratings
 552 after STN DBS (negative correlations) were observed in the right middle frontal gyrus
 553 (Brodmann area, BA 6). Correlations between increased cerebral glucose metabolism and
 554 increased ratings after STN DBS (positive correlations) were observed in the right posterior
 555 lobe of the cerebellum (Lobules VIII and VIIIb).

556

557 **Figure 3. Statistical parametric maps displaying correlations between decreased**
 558 **cerebral glucose metabolism and increased ratings (Images a, d, e and f) on the Neutral**
 559 **scale when patients listened to neutral stimuli (in blue), and between increased cerebral**
 560 **glucose metabolism and increased ratings (Images a, b, c and d) on the Neutral scale**
 561 **when they listened to neutral stimuli (in red) after STN DBS.**



562

563 *Note.* Significant differences ($p < .001$ corrected, $k > 70$ for cortical structures and $k > 25$ for
 564 subcortical and cerebellar structures) are shown in three orthogonal views. R: right
 565 hemisphere; L: left hemisphere.

566 3.5.2 Model 2: Ratings on Surprise scale for neutral stimuli

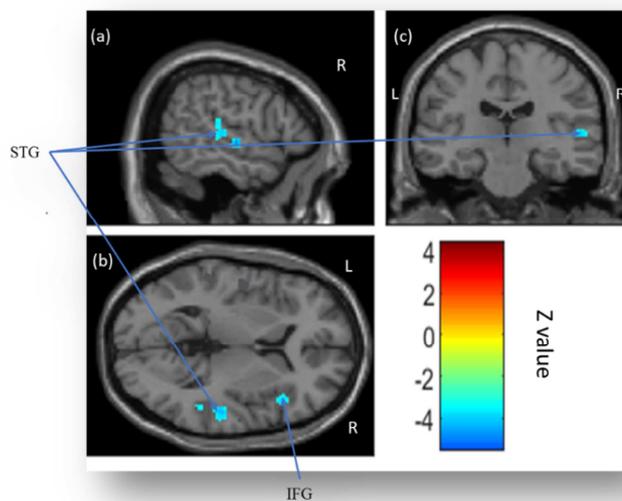
567 No significant correlations were observed.

568 3.5.3 Model 3: Ratings on Sadness scale for sadness stimuli (Fig. 4)

569 Correlations between decreased cerebral glucose metabolism and increased ratings
570 after STN DBS (negative correlations) were observed in the right superior temporal gyrus
571 (BA 41) and right inferior frontal gyrus (IFG) (BA 45). No significant correlations were
572 observed between increased cerebral glucose metabolism and increased ratings after STN
573 DBS (positive correlations).

574

575 **Figure 4. Statistical parametric maps displaying correlations between decreased**
576 **cerebral glucose metabolism and increased ratings (Images a, b and c) on the Sadness**
577 **scale when patients listened to sadness stimuli after STN DBS.**



578

579 *Note.* Significant differences ($p < .001$ corrected, $k > 70$) are shown in three orthogonal views.

580 IFG: inferior frontal gyrus; L: left hemisphere; R: right hemisphere; STG: superior temporal
581 gyrus.

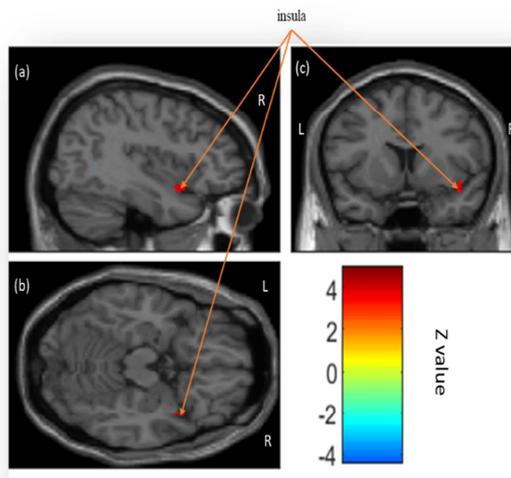
582

583 **3.5.4 Model 4: Ratings on Happiness scale for happiness stimuli (Fig. 5)**

584 No significant correlations were observed between decreased cerebral glucose
585 metabolism and increased ratings after STN DBS (negative correlations). Correlations
586 between increased cerebral glucose metabolism and increased ratings after STN DBS
587 (positive correlations) were observed in the right insula (BA 38).

588

589 **Figure 5. Statistical parametric maps displaying correlations between increased cerebral**
590 **glucose metabolism and increased ratings (Images a, b and c) on the Happiness scale**
591 **when patients listened to happiness stimuli after STN DBS.**



592

593 *Note.* Significant differences ($p < .001$ corrected, $k > 70$ for cortical structures and $k > 25$ for
594 subcortical and cerebellar structures) are shown in three orthogonal views. R: right
595 hemisphere; L: left hemisphere.

596

597 **3.5.5 Model 5: Ratings on Surprise scale for happiness stimuli**

598 No significant correlations were observed.

599

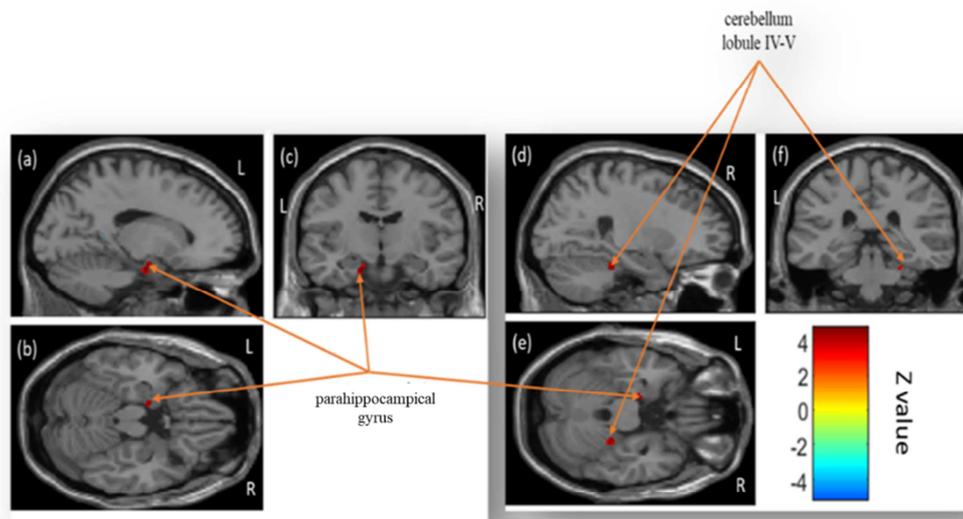
600

601 **3.5.6 Model 6: Ratings on Fear scale for fear stimuli (Fig. 6)**

602 No significant correlations were observed between decreased cerebral glucose
 603 metabolism and increased ratings after STN DBS (negative correlations). Correlations
 604 between increased cerebral glucose metabolism and increased ratings after STN DBS
 605 (positive correlations) were observed in the right anterior cerebellum (Lobules IV and V) and
 606 left parahippocampal gyrus (BA 35).

607

608 **Figure 6. Statistical parametric maps displaying correlations between increased cerebral**
 609 **glucose metabolism and decreased ratings (Images a, b, c, d, e and f) on the Fear scale**
 610 **when patients listened to fear stimuli after STN DBS.**



611

612 *Note.* Significant differences ($p < .001$ corrected, $k > 70$ for cortical structures and $k > 25$ for
 613 subcortical and cerebellar structures) are shown in three orthogonal views. R: right
 614 hemisphere; L: left hemisphere.

615

616 **4 DISCUSSION**

617 The aim of the present study was twofold: first, to investigate the effects of STN DBS
618 on the ability of patients with PD to recognize emotional prosody, and to correlate these
619 emotional prosody modifications with changes in cerebral glucose metabolism; *second*, to test
620 the impact of motor asymmetry on emotional prosody performances before and after DBS.
621 We therefore correlated the emotional prosody performances of 29 consecutive patients with
622 left- or right-sided PD motor symptoms who underwent STN DBS in pre- versus
623 postoperative conditions with modifications in cerebral glucose metabolism, as assessed with
624 ¹⁸F-DG-PET.

625 Based on Péron *et al.* (2013)'s model, we expected to observe impaired emotional
626 prosody recognition in the postoperative condition. These emotional modifications following
627 STN DBS would be correlated with glucose metabolism modifications in the cerebral network
628 that subtends emotional prosody, namely, the orbitofrontal cortex (OFC), IFG, auditory
629 cortex, basal ganglia, amygdala, and posterior cerebellum. In the light of Stirnimann *et al.*
630 (2018)'s results, we predicted that these emotional effects would be driven by a specific
631 subgroup of patients characterized by more left-sided motor symptoms (*i.e.*, with greater right
632 hemispheric brain dysfunction). Results partially confirmed these hypotheses, but also
633 revealed patterns of effects that were more complex than expected. An interaction between
634 STN DBS and motor lateralization had a differential impact on the performances of LPD *and*
635 RPD patients, resulting in two main patterns of effects.

636 **4.1 Dichotomization of effects**

637 The behavioral results could be grouped into two patterns of effect.

638 The *first* pattern was characterized by performances that seemed to *normalize*
639 postoperatively. This was the case for ratings on the target scales when participants listened to

640 neutral, happiness or anger stimuli, as well as on the nontarget Surprise scale when
641 participants listened to happiness stimuli. These effects were driven by the performances of
642 the LPD subgroup.

643 The *second* pattern was characterized by a postoperative *deterioration* in the ability to
644 recognize emotional vocal expressions, characterized by comparable performances across the
645 control and PD groups in the preoperative condition, but significantly different performances
646 in the postoperative condition for ratings on the Fear scale when participants listened to fear
647 stimuli. This effect was driven by the performances of the RPD subgroup.

648 As far as cognitive-metabolic correlations are concerned, interesting and partly
649 predicted results emerged. We found predicted correlations between modifications in
650 emotional prosody recognition and metabolic modifications in the right IFG, superior
651 temporal gyrus, insula and posterior cerebellum. However, the involvement of the left
652 perirhinal cortex (BA 35) and right middle frontal gyrus (BA 6) had not been predicted.

653

654 **4.2 Differential impact of STN DBS according to motor symptom asymmetry**

655 Overall, we observed that patients in the LPD subgroup exhibited a vocal emotional
656 impairment in the preoperative condition for neutral, sadness and happiness stimuli that STN
657 DBS seemed to normalize. By contrast, the surgery seemed to have a deleterious effect on
658 fear recognition abilities in the RPD subgroup of patients.

659 From our point of view, this pattern of results, while partly unexpected, can still be
660 interpreted in the context of Péron *et al.* (2013)'s model, and even seems to reinforce it.
661 Accordingly, RPD patients, who did not show any emotional impairment prior to surgery,
662 owing to the right hemispheric specialization of the basal ganglia during vocal emotion
663 processing (Stirnemann *et al.*, 2018), developed emotional impairment in the wake of DBS.
664 Just as dopathery can create an overdose effect on functionally intact circuits, so STN DBS

665 can desynchronize the limbic loop while at the same time re-synchronizing the activity of the
666 motor loop, as predicted by Péron *et al.* (2013)'s model. By contrast, LPD patients did display
667 vocal emotional impairment prior to surgery (in line with Stirnimann *et al.*, (2018), but STN
668 DBS seemed to normalize this deficit, through the functional re-synchronization of the limbic
669 loop, thereby restoring the necessary cerebral and cerebellar interactions needed for intact
670 vocal emotion processing.

671 The present results corroborate the notion of hemispheric specialization of the STN
672 during vocal emotion decoding, suggesting that the *right* STN plays a role in emotional
673 prosody processing. This is in line with three studies in patients with PD (Garrido-Vasquez *et al.*
674 *et al.*, 2013; Stirnimann *et al.*, 2018; Ventura *et al.*, 2012) that demonstrated an emotional
675 prosody processing impairment in LPD but not in RPD, compared with HC. It is also
676 congruent with a neuroimaging study in HC (Kotz *et al.*, 2003) that reported right but not left
677 basal ganglia activation by emotional prosody. Finally, our results are in line with two
678 intracranial event-related potential studies among patients with PD who had undergone DBS
679 that revealed heightened neural activity at the spike (Eitan *et al.*, 2013) and local field
680 potential (Péron *et al.*, 2017) levels in the *right* ventral STN, in response to emotional versus
681 neutral auditory material. STN DBS appears to have a differential impact, depending on the
682 lateralization of patients' motor symptoms and their baseline emotion perception abilities. The
683 metabolic results seem to go in the same direction, as we observed that the pattern of effects
684 primarily involving modifications in the RPD subgroup's performances (worsening)
685 correlated with metabolic modifications in the left hemisphere (i.e., parahippocampal gyrus),
686 while the pattern of results mainly involving modifications in the LPD subgroup's
687 performances (improvement) correlated with metabolic modifications solely in the right
688 hemisphere.

689 Accordingly, we believe that the literature in this domain should be reread in the light
690 of these new findings, and it may be that the divergent results that have sometimes been
691 reported, and which have fueled virulent debates in the scientific community (Péron, 2014),
692 can be attributed to the fact that analyses are generally conducted for the whole group, even
693 though the patients in question are actually quite heterogeneous. We observed an effect of
694 DBS on emotional prosody recognition at the *subgroup* level, and we can assume that studies
695 suggesting that there is no post-DBS effect are those that fail to take motor lateralization at
696 disease onset into account, thereby inducing a noneffect. For instance, a recent study
697 concluded that after STN DBS, the ability to recognize emotional prosody remains intact, and
698 only fear production is impaired (Jin et al., 2017). It is interesting to note that its results at the
699 whole group level were almost the same as ours (compare Supplementary Material Fig. SI 2
700 in this article with Fig. 1b in Jin et al., 2017). Had these authors analyzed their data separately
701 according to motor lateralization, we can speculate that the patterns of results would have
702 been different. Future studies should distinguish between patients on the basis of their motor
703 lateralization.

704 **4.3 Specificity of the emotions affected and potential STN involvement in embodiment** 705 **processes**

706 The question of the specificity of the emotions affected remains to be addressed. Why
707 does the recognition of some emotions deteriorate (here, fear) and that of others improve
708 (here, anger, happiness, neutral and sadness)? Our study was not designed to answer this
709 question, but previous results can shed light on it, notably regarding neutral emotion.

710 The case of neutral is very interesting. Our results replicated Mondillon et al. (2012)'s
711 results for the recognition of neutral, but unfortunately this study did not distinguish between
712 LPD and RPD patients. When Mondillon et al. (2012) explored the recognition of facial

713 emotions in patients with PD following STN DBS, they found that the patients in the
714 postoperative condition recognized neutral expressions better than the matched HC group did.
715 The authors interpreted their results in the context of simulation models (Niedenthal, 2007;
716 Niedenthal, Mermillod, Maringer, & Hess, 2010). The patients' amimia may have led them to
717 adopt a relatively neutral expression during the task. As a consequence, they recognized the
718 corresponding neutral faces *better* than HC did. We believe that the same hypothesis could
719 reasonably apply in the vocal modality, thus explaining the present results. Although it
720 remains to be demonstrated, we can hypothesize that vocal emotion recognition deficits in PD
721 should be interpreted in the context of impaired audio autofeedback. Dysarthrophonic
722 disorders in PD can affect the speech production subsystem (e.g., glottal-supraglottal
723 articulation system), but may also affect the laryngeal phonatory system and/or the pulmonary
724 system. Thus, we can also assume that minute movements in the larynx and other muscles
725 involved in speech articulation (inner speech processes or related processes; i.e.,
726 subvocalization processes) are affected, leading to increased misattribution in the recognition
727 of vocal emotions. Interestingly, previous studies have reported modifications in
728 velopharyngeal control and speech respiration following STN DBS (Hammer, Barlow, Lyons,
729 & Pahwa, 2010, 2011). In their discussion, Mondillon et al. (2012) could not rule out an
730 alternative explanation, whereby the answers given by patients with PD are *default responses*
731 that they give when they experience difficulty in an emotion recognition task. Interestingly,
732 our methodology featuring nontarget scales and continuous ratings (in contrast to the
733 categorical choices used in Mondillon et al.'s study), enabled us to exclude this alternative
734 explanation. The embodiment explanation was also corroborated by our metabolic results. At
735 the neural level, lesions in the right ventral primary and secondary somatosensory areas,
736 temporoparietal junction (Arzy, Thut, Mohr, Michel, & Blanke, 2006) and, to a lesser extent,
737 the insula and anterior supramarginal gyrus, have repeatedly been found to compromise

738 emotion recognition (Adolphs, 2002). One interpretation of these findings is that viewing
739 expressions of emotion triggers an emotional response in the perceiver that mirrors the
740 emotion depicted in the stimulus (Wild, Erb, & Bartels, 2001), and representing this
741 emotional response in somatosensory cortices in turn provides information about the emotion.
742 According to embodiment theories, by generating internal somatosensory representations of
743 perceived emotional stimuli, and thereby simulating socially relevant information, the
744 somatosensory cortices play a role in emotion recognition. To sum up, and in line with
745 Mondillon et al.'s propositions, we suggest that for the LPD subgroup of patients, whereas L-
746 DOPA *overdoses* the ventral stream of the OFC with dopamine in the preoperative condition,
747 DBS compensates for this overactivation by decreasing OFC activity, thereby restoring the
748 necessary OFC-amygdala interaction needed to preserve vocal emotion processing. This is
749 reinforced by the fact that their patterns of performances were correlated with LEDD, and is
750 corroborated by a previous report demonstrating the presence of dopaminergic overdose
751 effects in the context of vocal emotion recognition in PD (Péron, Grandjean, Drapier, &
752 Vérin, 2014). At the metabolic level, we were surprised not to observe correlations with a
753 network involving the OFC-amygdala pair. We only found significant effects in the right
754 middle frontal gyrus (BA 6) and right posterior lobe of the cerebellum (Lobules VIII and
755 VIIIb) (Fig. 3 and Table 6). This is, however, a very interesting result. First, regarding the right
756 premotor cortex, it is in line with the simulation hypothesis. Second, recent propositions have
757 been made regarding the cerebellum's involvement in the network that subtends embodied
758 cognition (Guell, Gabrieli, & Schmahmann, 2018) and in the affective domain. It has been
759 suggested that increased volumes in Crus 1 in persons with high alexithymic traits are related
760 to an altered embodiment process, leading to emotions that are not cognitively interpreted
761 (Laricchiuta et al., 2015). (Thomasson et al., 2019) recently demonstrated that patients with
762 chronic cerebellar ischemic stroke display vocal emotion deficits, compared with matched

763 HC, and these emotional misattributions are correlated with lesions in right Lobules VIIb,
764 VIIa,b and IX, corroborating the effects we observed for Lobules VIIb and VIII.

765 Regarding *fear*, it is interesting to note that studies reporting a significant deficit in
766 emotion recognition following STN DBS have often highlighted impairments for this
767 particular emotion. As mentioned previously, these effects may have been driven by RPD
768 patients (Biseul et al., 2005; Le Jeune et al., 2008). Unfortunately, this information is rarely
769 documented, and analyses would therefore need to be rerun on the raw data to take account of
770 this factor, which seems to be critical in the results.

771 **5 SUMMARY AND CONCLUSION**

772 Taken together, patients with predominantly left-sided motor symptoms (i.e., with
773 greater right hemispheric brain dysfunction; LPD) presented impaired vocal emotion
774 recognition in the preoperative condition for neutral, sadness and happiness stimuli that STN
775 DBS seemed to normalize. By contrast, surgery seemed to have a deleterious effect on fear
776 recognition abilities in the subgroup of patients with predominantly right-sided motor
777 symptoms (i.e., with greater left hemispheric brain dysfunction; RPD). The behavioral
778 improvement observed in LPD patients was correlated with metabolic modifications in a
779 right-lateralized network known to be involved in emotional prosody recognition (i.e., right
780 IFG, superior temporal gyrus, insula, and posterior cerebellum), while the behavioral
781 worsening effect among RPD patients was correlated with metabolic modifications in the left
782 parahippocampal gyrus and right cerebellum.

783 The present results corroborate the notion of hemispheric specialization of the STN
784 during vocal emotion decoding and the differential impact of STN DBS according to PD
785 motor symptom asymmetry, and raise the question of the potential involvement of this basal
786 ganglion in embodiment processes.

787

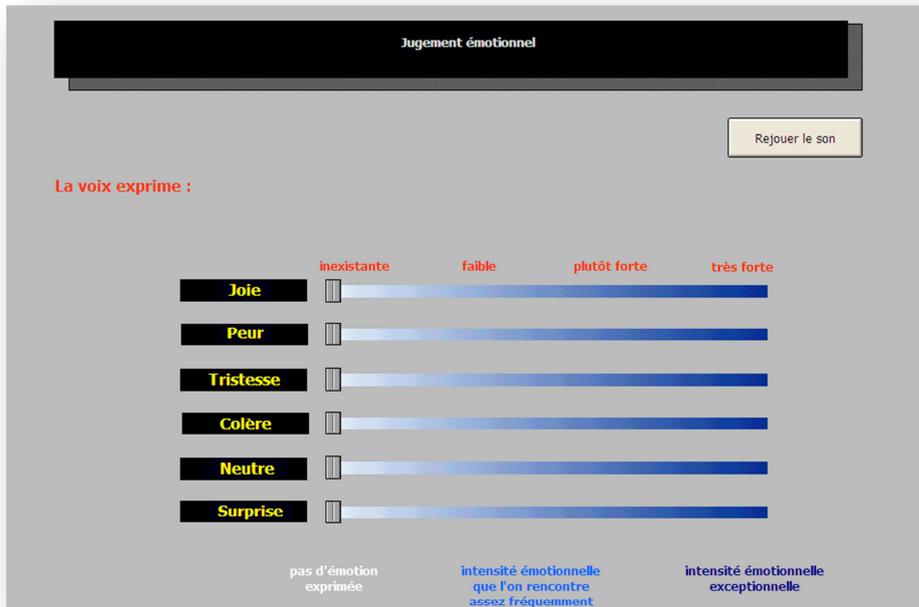
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- 976

977 **APPENDIX**978 **Computer interface for the original emotional prosody recognition**979 **paradigm**

980

981 *Note. Joie = Happiness, Peur = Fear, Tristesse = Sadness, Colère = Anger, Neutre = Neutral,*982 *Surprise = Surprise, Pas d'émotion exprimée = No expressed emotion, Intensité émotionnelle*983 *que l'on rencontre assez fréquemment = Emotional intensity we quite often encounter,*984 *Intensité émotionnelle exceptionnelle = Exceptional emotional intensity.*

Running head: Vocal emotion and STN DBS in PD

Title : Motor symptom asymmetry in Parkinson's disease predicts emotional outcome following subthalamic nucleus deep brain stimulation

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Highlights

- Emotional prosody recognition in PD patients before and after DBS is explored
- A post-DBS *worsening* effect for patients with more right motor symptoms
- A post-DBS *improving* effect for patients with more left motor symptoms
- Improving effect correlated with modifications in a right limbic network
- Worsening effect correlated with modifications in the left parahippocampal gyrus