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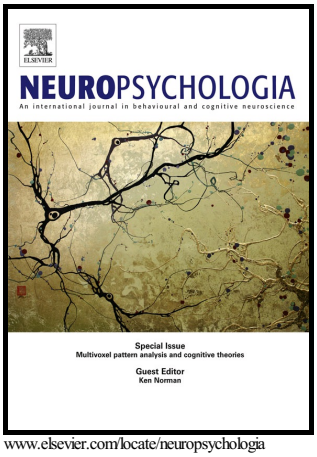

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Subthalamic deep brain stimulation influences complex emotional musical experience in Parkinson's disease

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Abstract

Subthalamic deep brain stimulation (STN DBS) is an effective treatment for reducing the motor symptoms of patients with Parkinson's disease (PD), but several side effects have been reported, concerning the processing of emotions. Music has been shown to evoke powerful emotional experiences - not only basic emotions, but also complex, so-called *aesthetic experiences*. The goal of the present study was therefore to investigate how STN DBS influences the experience of both basic and more complex musical emotions in patients with PD. In a three-group between-participants design, we compared healthy controls (HC), patients receiving STN DBS (PD-DBS), and patients who were candidates for STN DBS and receiving medication only (PD-MO) on their assessments of subjectively experienced musical emotions. Results showed that in general, the experience of musical emotions differed only marginally between the PD-MO, PD-DBS, and HC groups. Nonetheless, we were able to discern subtle but distinct effects of PD and

[1] These authors contributed equally to this work

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STN DBS in the emotional responses. Happy music, for instance, seemed to induce a heightened experience of negative emotions (tension) in PD-MO patients. STN DBS appeared to normalize this particular effect, but increased nostalgic feelings - a rather complex affective experience – in response to the same emotional stimuli. This should not be taken as indicating a bias for nostalgia in the PD-DBS subgroup, as these patients found music inducing melancholy to be less nostalgic and more joyful than HC did. In conclusion, our study showed that music elicits slightly altered emotional experiences in patients with and without STN DBS. In particular, STN DBS seems to induce less distinct emotional responses, blurring the boundaries between complex musical emotions.

Keywords

Emotion, music, subthalamic nucleus, deep-brain stimulation, Parkinson

1 Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that affects the basal ganglia circuits, generating not only motor symptoms, but also cognitive and affective impairments (Peron et al., 2012). As the deterioration in the basal ganglia progresses, these patients experience increasing neuropsychiatric difficulties that can eventually lead to dementia. Even in the earlier stages, cognitive and emotional impairments can be observed. For example, patients with PD reportedly have difficulty recognizing emotions in facial expressions and emotions expressed through music (see Lima et al., 2013; Saenz et al., 2013; van Tricht et al., 2010).

High-frequency deep brain stimulation of the subthalamic nucleus (STN DBS) has become one of the most effective treatments for improving the motor symptoms of PD (Fasano et al., 2010; Kleiner-Fisman et al., 2006; Limousin et al., 1998, 1995). STN DBS is a choice of treatment in cases in which Anti-Parikinsonian medication is not sufficient to control motor symptoms. However, many clinical studies have reported negative nonmotor side effects following STN DBS surgery. These side effects include cognitive (e.g., impaired verbal memory) and behavioural or emotional impairment (e.g., apathy or hypomania) (Kumar et al., 1998; Perriol et al., 2006; Temel et al., 2006). STN DBS-induced emotional impairment has been shown to concern the recognition of emotional

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facial expressions, selectively affecting negative emotions (Drapier et al., 2008; Dujardin et al., 2004; Péron et al., 2010a; Schroeder, 2004), and the recognition of emotions induced by voices, with deficits for both negative and positive emotions (Péron et al., 2010b). In these studies, the impairments could not be attributed to additional deficits such as depression or general cognitive decline.

Emotional impairment after STN DBS also affects subjective feelings, or emotional subjective experience. Patients who have to adjust their own emotional state to perceived facial expressions report an enhanced mood induction effect in the ON versus OFF stimulation condition (i.e., when the STN stimulator is turned on or off) (Schneider et al., 2003). Patients have also been shown to attribute more negative valence to pictures featuring erotic, food or aversive content when they are stimulated (Serranová et al., 2011). When they see film excerpts selected to induce anger, happiness, sadness, fear, or disgust, postoperative patients report significantly less intense feelings of sadness and fear for the excerpts validated to arouse these two emotions, compared with pre-operative and control groups (Vicente et al., 2009). The direction in which performances are modulated by STN DBS varies across studies, owing to their different designs, but all the results nonetheless point to a role of the STN in emotional subjective experience.

This influence is attributed to the neuroanatomical organization of the basal ganglia, as the STN seems to play a key role in the limbic cortico-basal ganglia-thalamocortical circuit. It has been demonstrated that the STN can be functionally divided into motor, limbic and associative regions (Parent & Hazrati, 1995). It is therefore involved in the processing of motor information, but also associative and limbic information. The motor region, which lies in the dorsolateral territory of the STN, is the sole neurosurgical target of DBS in the treatment of Parkinsonian motor symptoms such as rigidity, akinesia and tremor. Emotional changes after STN DBS have been related to disturbance of the STN's limbic region, which lies in the medial territory of the STN. Neurons of the medial portion of the STN that belong to the limbic circuit specifically project to the ventral pallidum and ventral tegmental area (VTA), allowing the STN to influence the dopaminergic mesolimbic pathway. Afferents of these neurons come from limbic cortical areas (anterior cingulate cortex, orbitofrontal cortex (OFC)), the accumbens nucleus, the ventral pallidum and the VTA (Parent & Hazrati, 1995). The STN can therefore influence

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structures crucial to emotional processing, as has been highlighted in neuroimaging studies. Hilker et al. (2004) demonstrated that DBS STN can restore glucose metabolism in limbic and associative territories in the frontal lobe. Moreover, studies have shown that impaired recognition of facial emotions correlates with modifications in the cerebral glucose metabolism of the right OFC after bilateral STN-DBS (Le Jeune et al., 2008). Similarly, the disgust induced by a film excerpt decreases after DBS, while cerebral glucose metabolism in the bilateral prefrontal cortices, bilateral insula and right cerebellum increases (Ory et al., 2015). Studies examining local field potentials (LFPs) in patients with STN-DBS have reported increased activity in the limbic region of the STN in response to emotionally arousing versus neutral stimuli (Kühn et al., 2005), and a specific modulation of the right STN in response to angry and happy prosodies (Péron et al., 2017). The more specific involvement of the STN's ventral territory in the limbic circuit has been highlighted in studies showing that stimulation targeting this ventral portion induces an increase in emotional experience (Benedetti et al., 2004; Greenhouse et al., 2011).

The STN's role in the limbic circuit is one possible explanation for why modulation of its activity, particularly by DBS, leads to emotional alterations (see Péron et al., 2013, for a review). It should be borne in mind that STN-DBS often exceeds the motor territory, given the large size of the electrodes and the small size of the STN. The emotional alterations brought about by STN-DBS concern several of the emotional components identified in the component process model (Scherer, 2001). Emotion is defined as an episode of interrelated, synchronized changes in the state of all or most of the five components, occurring in response to the evaluation of an external or internal stimulus event considered relevant for the organism. These five components are cognitive, peripheral efference, motivational, motor expression and subjective feeling. Subjective feelings, or *qualia*, are conceptualized as the central component, which integrates all other components of emotion and is regarded as the conscious representation of emotional processes (Grandjean et al., 2008; Sander et al., 2005). In this study, we explored the impact of STN-DBS on subjective emotional experiences in patients with PD. These were induced via the auditory sensory modality, notably through music. This

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was the first time that the impact of DBS stimulation on subjective emotional experience had been tested for musical emotions.

Music is present in every known human culture, but the intense degree of pleasure associated with listening to music remains a mystery. The modification of emotions brought about by music is reported as the most important reason why people listen to music (Koelsch, 2010; Krumhansl, 1997). Music therefore seems to represent a powerful emotion-eliciting stimulus and an efficient research tool for studying emotions, as it allows strong, reproducible, positive and negative emotions to be induced in the laboratory (Koelsch, 2010). In short, music provides one of the most effective nonintrusive means of mood induction. It has become a standard mood induction method, and since the 1980s, more than 40 articles published in psychological journals have used this method (Västfjäll, 2002). The majority of these studies used music without words, especially classical music, as the affective content of the lyrics can have a crucial impact on the emotions that are induced (Stratton & Zalanowski, 1994). Moreover, classical music is reputed to elicit particularly intense emotions (Sloboda, 1991). Studies have usually focused on how listeners perceive or recognize the emotions expressed in music, which does not necessarily mirror what the listeners are feeling themselves (Juslin & Vastfjall, 2008). Whereas the emotions expressed by music rely mostly on the arrangement of musical features over time, the emotions experienced by listeners can be triggered by many factors, including not just the structural features of the music, but also the listeners' features (e.g., their mood and psychological state, memories and previous listening experiences), performance and contextual features, and cultural conventions (Scherer & Coutinho, 2013; Scherer & Zentner, 2001). Thus, the emotions expressed by the music and the emotions felt by the listeners may differ, and it is important to take this distinction into account when instructing listeners to report their emotional responses to music (Scherer, 2004). Because music does not seem to have goal implications, some researchers have claimed that it cannot induce emotions related to survival functions (Kivy, 1990) or indeed any emotions at all (Konecni, 2008, 2003). Others, like Scherer and Zentner, suggest that the emotions induced by music are not like basic or everyday emotions, such as anger, fear, sadness, joy, shame, disgust or guilt (Scherer, 2004; Zentner et al., 2008). Instead, these authors distinguish between utilitarian and aesthetic

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emotions (Scherer and Zentner, 2008). *Utilitarian emotions* are triggered by the need to adapt to specific situations that are important for an individual's goals and wellbeing, and they are usually highly intense, preparing the individual for action. *Aesthetic emotions* occur in situations where there are no consequences for survival, and represent more an appreciation of the intrinsic qualities of a piece of art. This does not mean that musical emotions cannot bring about behavioural or physiological modifications. Indeed, aesthetic experiences may sometimes be very intense, such as chills, thrills, tinkling of the spine, and tears (Konecni, 2003; Salimpoor et al., 2011). Given that musical emotions are, however, likely to induce a particular range of emotions (e.g., common basic emotions, such as anger or disgust, are typically not induced by music), Zentner and colleagues (2008) developed the Geneva Emotional Musical Scale (GEMS), covering the broad spectrum of affective states that can be experienced in response to music. These authors characterized music-induced emotions in four interrelated studies. They first compiled a list of music-relevant emotion terms and studied the frequency of both felt and perceived emotions. Gradually, through the use of a larger sample of listeners, they obtained a 9-dimensional model of music-induced emotions. This model proved to account for music-elicited emotions better than the basic emotion and dimensional emotion models that classify emotions along the arousal and valence dimensions (Russell, 2003). It has also already been used in a functional neuroimaging study that investigated the brain correlates of the different musical emotions it identifies (Trost et al., 2012). The authors found activation of the left striatum and insula for the emotional categories *wonder* and *joyful activation*, the right striatum and OFC for *nostalgia* and *tenderness*, the sensory and motor cortices for *tension*, *power* and *joy*, and ventromedial prefrontal cortex and hippocampus for *peacefulness*, *nostalgia* and *sadness*. More recently, the GEMS has also been studied in a clinical context. When Choppin et al. (2016) investigated emotional alterations in patients with bipolar disorder in response to music, they found that patients in a euthymic state experienced music inducing wonder as more negative than controls did (Choppin et al., 2016).

The aim of the present study was to explore subjective emotional experiences in response to music in PD and, for the first time, to quantify the impact of STN-DBS on these experiences, in order to investigate how PD - and also STN-DBS as PD

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treatment - influences patients' emotional lives. Music is an important emotional stimulus in everyday life, and impairment of the richness of the emotional experience could potentially affect patients' quality of life. In our study, musical emotions were evoked in two subgroups of patients with PD (candidates for STN-DBS and patients receiving STN-DBS stimulation), and an HC group. Comparison of these groups' self-assessments on the GEMS allowed us to study how patients' emotional experiences in response to music differ from those of healthy listeners, and to characterize the impact of STN-DBS on musically induced subjective emotional experience. In particular, we were interested in studying whether PD patients with or without STN-DBS would show any abnormal emotional responses to certain emotional categories, and/or would use emotional labels differently when assessing their emotional experiences.

2 Materials and methods

2.1 Patients

Two subgroups of 18 patients with PD (nine women) and one group of 18 healthy controls (nine women) were enrolled in our study. Patients were recruited at Rennes University Hospital. They had all been diagnosed with idiopathic PD and met the clinical criteria of the United Kingdom Parkinson's Disease Society Brain Bank (Gibb & Lees, 1988). The preoperative subgroup (PD-MO) included patients with advanced PD who were candidates for STN-DBS and who received as best medical treatment medication only. The postoperative subgroup (PD-DBS) included patients with advanced PD who were already undergoing bilateral STN-DBS. These patients were assessed between 28.1 and 33.8 months after surgery. Standard selection and exclusion criteria for surgery were applied to all patients (Welter et al., 2002). They presented motor fluctuations and dyskinesia that could not be controlled with standard oral medication, and baseline MRI scans excluded significant vascular abnormalities and brain atrophy. All participants met the following clinical inclusion criteria: no severe cognitive impairment documented by a Mattis Dementia Rating Scale (MDRS; Mattis, 1988) score over 130, no psychiatric history or other neurological disease, and no auditory impairment. There was no selection on musical expertise, but strong contempt of classical music was an exclusion criterion.

HC were recruited from the population of Rennes and matched with the PD-MO group for age and education level. Written informed consent was obtained from each

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participant.

2.2 Motor assessments

Each patient was scored on Part III of the Unified Parkinson's Disease Rating Scale (UPDRS-III; Fahn & Elton, 1987) in the on-drug state, the Hoehn and Yahr Scale (Hoehn & Yahr, 1967), and the levodopa equivalent daily dose (milligrams of L-DOPA and dopamine agonists taken by a patient per day) for the period during which they took part in the study.

2.3 Neuropsychological, psychiatric and auditory assessment

All participants underwent a battery of neuropsychological tests assessing their cognitive efficiency and executive functioning. This battery included the MDRS (Mattis, 1988), Trail-Making Test (Reitan, 1958), Stroop test (Stroop, 1935), verbal fluency tasks (phonemic and semantic) (Cardebat et al., 1990), and Modified Card Sorting Test (MCST; Nelson, 1976). The Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) was used for the psychiatric assessment. The absence of auditory impairment was confirmed with the Protocole d'Evaluation des Gnosies Auditives (PEGA; Agniel et al., 1992), in which participants had to discriminate between two sounds on pitch, intensity and timbre.

2.4 Surgical procedure

Quadripolar deep brain stimulation electrodes (Medtronic, Minneapolis, MN, USA) were implanted bilaterally in the STN using MRI-based targeting of the nucleus. Implantation was done under local anaesthesia, in the off-drug condition. Electrode placement was optimized through assessment of the clinical response to DBS and microrecordings (Benabid et al., 2009, 2000).

2.5 Musical stimuli

The stimuli consisted of 12 excerpts of instrumental music from the previous four centuries, taken from commercially available CDs (see Supplementary material, Table 1). This set of stimuli was derived from a previous study (Trost et al., 2012) and had already

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been used in the same format in another study (Choppin et al., 2016). The choice of excerpts avoided extremely popular pieces from the classical music repertoire, in order to reduce potential biases stemming from memory and semantic knowledge associated with the music. As in the study by Trost and colleagues (2012), each excerpt lasted for 45 seconds. This duration was chosen to allow enough time for the emotion elicitation process. The musical stimuli had been assessed in a preliminary behavioural rating experiment with a group of 20 healthy participants, to evaluate their ability to induce the different emotions. In this preliminary study, the stimuli were first assessed using the nine GEMS emotion categories. In a second step, with another group of 20 healthy participants, this assessment was confirmed with a short version of the GEMS featuring only four emotion categories: power, tension, wonder (GEMS categories wonder + joyful activation) and melancholy (GEMS categories nostalgia + sadness). Each of the 12 selected stimuli belonged to one of the four categories, resulting in three musical stimuli per category (see Supplementary Table 1). This preliminary study showed that each of the three excerpts per category consistently induced the target emotion.

According to Trost and colleagues (2012), the GEMS categories can be arranged in the two-dimensional circumplex arousal-valence space (Russell, 2003), allowing each GEMS emotion term to be attributed a certain degree of valence (defined as how pleasant an emotion is) and a certain degree of arousal (defined as how exciting an emotion is). Accordingly, in the short version, *power* could be described as an emotion category of high arousal and high valence, *tension* as one of high arousal and low valence, *wonder* as one of medium arousal and high valence, and *melancholy* as one of low arousal and medium valence.

In the present study, we used two series of 12 excerpts. Series A and Series B were counterbalanced across participants. These two series differed in the order of presentation of the excerpts. Moreover, each of the 12 excerpts in the two series was taken from the same musical piece, but a different section. The preliminary study showed that both excerpts of the same piece evoked the target emotion equally well.

2.6 Emotion elicitation procedure

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Patients were in the on-drug condition (and on-stimulation condition for the PD-DBS subgroup). The emotion elicitation procedure and set of stimuli had already been used in a previous publication (Choppin et al., 2016). For the emotion elicitation procedure, participants were each asked to listen to 12 musical excerpts each. Before each excerpt, they were instructed to listen attentively to the stimulus, and to keep their eyes closed. After each excerpt, they were asked to complete a short questionnaire probing the intensity of their emotional experience for each of the nine GEMS emotional categories: Tension, Wonder, Joyful activation, Nostalgia, Peacefulness, Tenderness, Transcendence, Power, and Sadness. Each emotion label was presented with two descriptive adjectives to clarify its meaning (see Supplementary Table 2). The order of the emotion terms in the list was always the same. Participants rated their emotional experience in response to each excerpt on all nine emotion labels, by moving a cursor along a continuous visual analogue scale ranging from *Not at all* to *Very much*. After rating an excerpt, participants relaxed for at least 20 seconds, during which they were asked to close their eyes, in order to return to an emotional baseline. Before the experiment, it was emphasized to participants that they should answer the questionnaire only regarding their own felt emotions, and not according to what the music expressed. Participants were asked to answer spontaneously, but without any time limit.

2.7 Statistical analyses

Comparative analyses of the groups' descriptive variables (demographic characteristics, psychiatric and neuropsychological assessments) were performed with the nonparametric Kruskall-Wallis test. Data concerning patients only were analysed with the Mann-Whitney test.

To test the experience of music-induced emotions in HC and patients with or without DBS, we ran generalized linear mixed models (GLMMs), with group (PD-MO, PD-DBS, HC) and scale (nine emotion categories) as fixed effects. We entered the variables *participant* and *musical excerpt* as random effects in the model, to take account of the interindividual variability in the way participants rated the scales and the variability in the emotions induced by the musical excerpts.

First, all four types of emotional stimulus were analysed in a single model, to test

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whether the groups' emotion assessments differed for all types of stimuli and all emotion scales. Second, we ran separate analyses for each type of stimulus (*melancholy*, *power*, *tension*, *wonder*), to investigate whether the three groups evaluated a given type of stimulus differently across the emotion scales. Here, we wanted to investigate whether the emotional responses to certain stimulus types differed across the groups. Third, we ran analyses for each emotional scale (Tension, Wonder, Joyful Activation, Nostalgia, Peacefulness, Tenderness, Transcendence, Power, Sadness), to test whether the three groups experienced a given emotional category differently across the different stimuli. The goal of this analysis was to see whether any of the groups employed emotional labels differently when evaluating their emotional experiences.

Statistical analyses were performed using RStudio (Version 0.97.551) for the GLMMs, based on R (Version 3.0.1). The significance threshold was set at $p = .05$. Bonferroni corrections of the significance level were adopted to account for multiple comparisons. The significance threshold was set at $p = .0125$ for the analyses for each stimulus type, and at $p = .0056$ for the analyses for each individual scale.

The emotion assessment data were visually inspected for potential outliers. However, none of the participants was excluded because of unusual response patterns, as unusual responses did not seem to occur systematically.

We performed additional analyses to test the impact of other interindividual differences that could potentially confound the results. First, we investigated whether the patients' dopaminergic treatment influenced the results. To this end, we ran two separate analyses that only included the patients. We tested whether dopamine had an impact on the triple interaction between stimulus type, scale, and group. Furthermore, we tested whether there was a quadruple interaction between dopamine, stimulus type, scale, and group. Analyses showed no impact of dopamine on the triple interaction, and there was no quadruple interaction with dopamine, indicating that dopamine had no influence on the evaluations. Therefore, no further analyses were performed including the dopamine variable. Second, we analysed interindividual differences in familiarity with the music. The degree of familiarity with the music did not differ significantly between the groups ($p > 0.4$), and adding familiarity to the models as a covariate did not change the results. We therefore

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conclude that the results for emotional experiences were not influenced by interindividual difference in familiarity with the music.

3. Results

3.1 Demographic, clinical and neuropsychological characteristics

Demographic and clinical data are provided in Table 1. There were no significant differences between the PD-DBS, PD-MO, and HC groups on either age (H = 1.63, p = .44) or education level (H = 3.43, p = .18). The patients' relatively young age meant that the other comorbidity factors and cognitive deficits that often occur as the disease progresses had less of an effect. There were no significant differences between the two patient subgroups on either disease duration (U = 106, p = .08) or the UPDRS-III motor score, assessed in the on-dopa condition and, for the PD-DBS subgroup, the OFF stimulation condition group (U = 107, p = .08).

Table 1: Demographic and clinical characteristics of the patient and HC groups.

Variable	**Healthy controls (HC)**	**Preoperative patients (PD-MO)**	**Postoperative patients (PD-DBS)**	
	Mean (*SD*)	**Mean (*SD*)**	**Mean (*SD*)**	***p* value**
Age in years	57.2 (9.8)	55.1(9.1)	58.5(6.2)	.44†
Education in years	12.,8 (3.7)	12.2(4.2)	10.7(3)	.18†
Disease duration in years	N/A	11.6(3.6)	14.3(4.3)	.08††
Levodopa equivalent dose in mg/day	N/A	1297.3(522.8)	627.2(316.6)	.0001††
UPDRS-III motor score[a]	N/A	11.2(8.5)	15.6(9.3)	.08††
Hoehn and Yahr score [b]	N/A	0.8(0.9)	0.9(1)	1††

Note. N/A =Not applicable.
a Values obtained in the on-dopa condition for both PD subgroups, and with the stimulator turned off in the DBS subgroup.
b In the on-dopa condition
† Kruskal–Wallis test.
†† Mann–Whitney test.

Psychiatric and neuropsychological assessment data are set out in Table 2. The three groups had comparable scores on the MDRS (H = 2.21, p = .33), Stroop interference test (H = 2.18, p = .34), Trail-Making Test (H = 3.21, p = .2), MCST (H = 4.16, p = .12), and phonemic (letter *p*) (H = 2.44, p = .29) and semantic (animals) (H = 1.47, p = .48) fluency tests. For the psychiatric assessment, there were no significant differences between the groups on the MADRS (H = 3.35, p = .19).

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All participants scored above 7/10 on the PEGA, which excluded any hearing impairment.

Table 2: Performances of the patient and HC groups on the psychiatric and neuropsychological tests.

Variable	Healthy controls (HC)	Preoperative patients (PD-MO)	Postoperative patients (PD-DBS)	
	Mean (*SD*)	**Mean (*SD*)**	**Mean (*SD*)**	***p* value**
MADRS	2.88(2.91)	5.39(3.82)	4.39(4.02)	.19†
Stroop interference	3.45(9.5)	1.07(6.74)	0.16(6.92)	.34†
TMT B-A	39.11(20.44)	51.17(30.28)	65.94(61.99)	.2†
MCST cat.	5.72(0.57)	5.82(0.5)	5.05(1.47)	.13†
MCST pers.	1.11(1.53)	1.12(1.36)	2.83(3.49)	.27†
MDRS	141(2.57)	139.6(3.4)	139.2(4.08)	.33†
Phonemic fluency	25.22(8.98)	21(8.4)	21.17(7.75)	.29†
Semantic fluency	32.72(6.94)	33.39(7.21)	29.22(10.65)	.48†

Note. MADRS = Montgomery-Åsberg Depression Rating Scale; TMT B-A= time difference between completion of Parts B and A of the Trail-Making Test; MCST cat. = number of categories achieved in the Modified Card Sorting Test; MCST pers. = number of perseverative errors in the Modified Card Sorting Test; MDRS =Mattis Dementia Rating Scale.
† Kruskal–Wallis test.

3.2 Evaluation of subjective emotional experiences

The general analysis including all stimulus types and all scales did not reveal any significant interaction between group, type of stimulus, and emotion scale (for means and standard deviations, see Supplementary Table 3). This indicates that, in general, emotional experiences did not differ substantially between the HC, PD-MO and PD-DBS groups. Nonetheless, we performed additional analyses to investigate further whether emotional assessments differed between the groups for specific types of stimulus or emotion scales. In these separate analyses, we adopted a conservative Bonferroni correction of the significance threshold, to identify robust differences between the three groups on emotional experiences.

In the first series of separate analyses, we tested whether HC, PD-MO and PD-DBS differed in the intensity of their emotional reactions to certain types of emotional stimuli (*melancholy*, *power*, *tension*, *wonder*).

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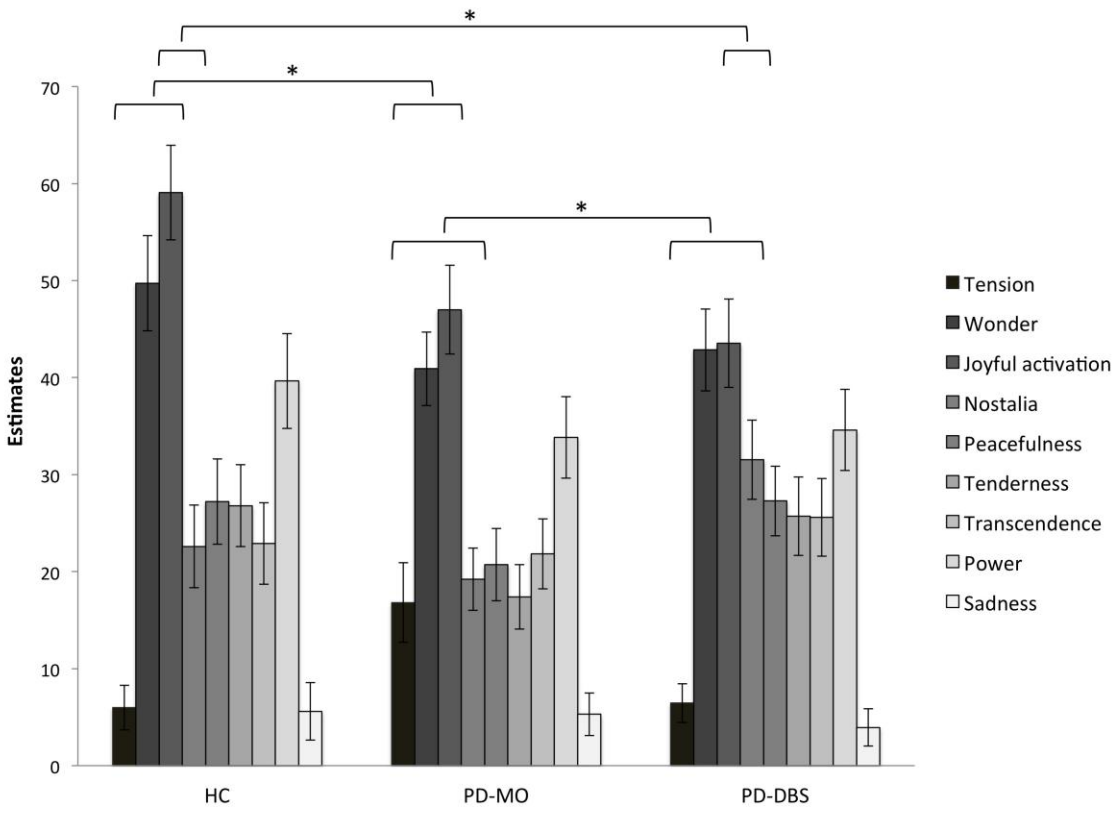

Figure 1: Ratings of the *wonder* stimulus type on the different emotion scales. Estimates of the means are displayed with standard errors.

Running a separate analysis for each type of stimulus revealed a significant main effect of scale for each stimulus type: *melancholy*, $F(8, 1391.95) = 48.70$, $p < .001$; *power*, $F(8, 1391.90) = 79.51$, $p < .001$; *tension*, $F(8, 1391.79) = 25.00$, $p < .001$; and *wonder*, $F(8, 1391.88) = 61.94$, $p < .001$. There was no main effect of group for any of the four stimulus types. A significant interaction between group and scale was only observed for *wonder* excerpts, $F(16, 1375.84) = 2.22$, $p = .0036$. As the interaction between the scale and group was significant for this type of stimulus, we ran further post hoc tests with a Bonferroni-corrected significance threshold of $p = (.05/9 \times 4 \times 3) = .00046$. These tests revealed significant differences between the HC and PD-DBS groups on Joyful activation and Nostalgia assessments, $\chi^2(1, N = 54) = 14.46$, $p < .001$, between the HC and PD-MO groups on Tension and Joyful activation assessments, $\chi^2(1, N = 54) = 12.67$, $p < .001$, and between the PD-MO and PD-DBS subgroups on Tension and Nostalgia assessments,

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$\chi^2(1, N = 54) = 12.43, p < .001$ (see Fig. 1). These results indicated that differential emotional experiences between the groups could only be observed in response to musical excerpts inducing *wonder*. The comparison between HC and PD-MO showed that the disease had the effect of reducing the difference in intensity between felt Tension and Joyful activation. STN-DBS had a normalizing effect, for whereas there was no difference in the intensity of felt Tension and Nostalgia in response to *wonder*-inducing music in the PD-MO group, it was more differentiated in the PD-DBS group. By contrast, *wonder* stimuli induced feelings of Joyful activation and Nostalgia that were more similar in intensity in the PD-DBS group than in the HC group, where these stimuli evoked far stronger feelings of Joyful activation than of Nostalgia.

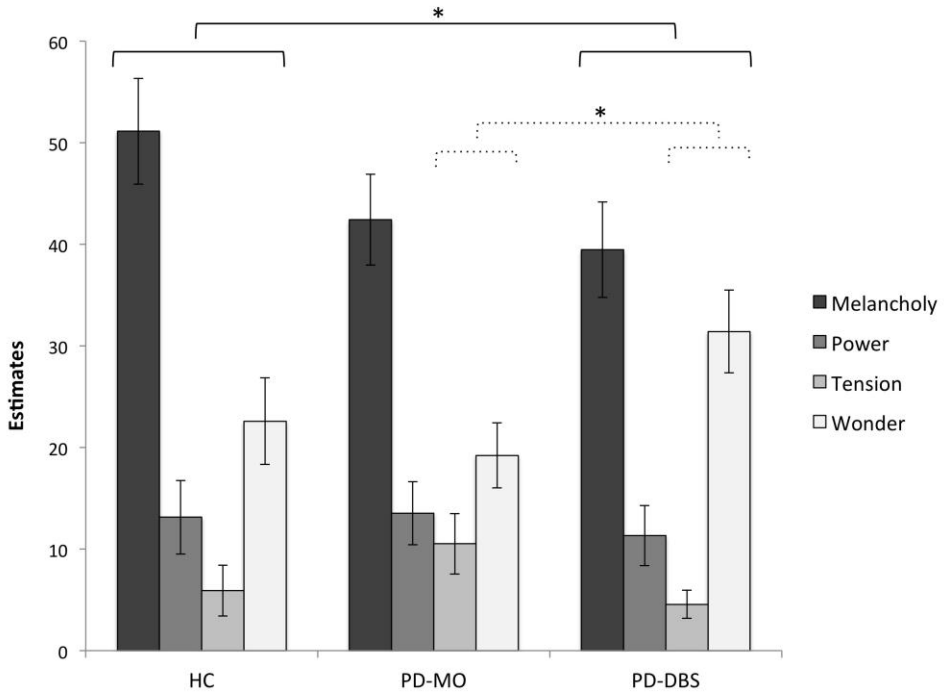

Figure 2: Nostalgia ratings for the different stimulus types. Estimates of the means are displayed with standard errors. Dashed lines indicate a trend.

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In the second series of analyses, we investigated whether HC, PD-MO and PD-DBS differed in their experience of the musical GEMS emotions (Tension, Wonder, Joyful activation, Nostalgia, Tenderness, Peacefulness, Transcendence, Power, Sadness) across the four types of stimuli. These analyses revealed significant main effects of stimulus type for each scale: Tension, $F(3, 19.61) = 11.78$, $p < .001$; Wonder, $F(3, 18.91) = 14.13$, $p < .001$; Joyful activation, $F(3, 19.40) = 14.32$, $p < .001$; Nostalgia, $F(3, 19.77) = 36.55$, $p < .001$; Peacefulness, $F(3, 19.35) = 34.40$, $p < .001$; Tenderness, $F(3, 19.49) = 15.70$, $p < .001$; Transcendence, $F(3, 19.10) = 14.23$, $p < .001$; Power, $F(3, 19.56) = 31.71$, $p < .001$; and Sadness, $F(3, 19.52) = 10.14$, $p < .001$. No main effect of group was found for any of the nine scales. Only for the Nostalgia scale did we find a trend towards a significant interaction between group and stimulus type, $F(6, 566.58) = 2.914$, $p = .0083$. We then performed post hoc tests with a Bonferroni-corrected significance threshold of $p = (3 \times 2 \times 3) = .0028$. These tests revealed significant differences between the HC and PD-DBS groups on their assessments of *melancholy* and *wonder* stimuli, $\chi^2(1, N = 54) = 10.93$, $p = .00095$, and a trend towards a significant difference between the PD-MO and PD-DBS groups on their assessments of *tension* and *wonder* stimuli, $\chi^2(1, N = 54) = 8.58$, $p = .0034$ (see Fig. 2).

These results indicate that the only emotion the three groups experienced differently across the musical stimuli was Nostalgia. An effect of PD could not be identified, as there were no significant differences between the HC and PD-MO groups. The effect of STN-DBS tended towards significance, in that the stimuli inducing *tension* and *wonder* evoked similar levels of Nostalgia in the PD-MO group, whereas in the PD-DBS group, the *wonder* stimuli induced more Nostalgia than the *tension* stimuli did. We again found a difference between the HC and PD-DBS groups, for whereas HC clearly rated *melancholy* stimuli as inducing more Nostalgia than the *wonder* stimuli did, the PD-DBS group experienced more or less the same levels of Nostalgia in response to *melancholy* and *wonder* stimuli.

4. Discussion

The goal of the present study was to investigate how emotional responses to music are altered by PD and by one of its treatments, STN-DBS. In particular, we wanted to study the effects of PD and STN-DBS on the experience of musical emotions by comparing

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assessments of subjectively experienced musical emotions produced by HC, patients with PD who were under medication only, and patients with PD who were received STN-DBS. In general, we observed that subjective experiences did not differ extensively between the groups, as the triple interaction between group, type of stimulus and emotion scale was not significant. Moreover, none of the analyses revealed a significant main effect of group, indicating that, across all stimulus types, none of the emotions was more strongly experienced by any of the three groups. Thus, there were no generally attenuated emotional responses in any of the groups, from which we can infer that emotional intensity was similar across all three. Nor did we find that any particular musical emotion stood out in the emotional experiences of any group. This result can be regarded as an indication that emotional experiences in response to music remained intact, despite the disease and the nature of its treatment. However, despite the nonsignificant triple interaction, given our clinical experience with patients and the literature on impaired emotional recognition and experience in response to affective stimuli (Lima et al., 2013; Péron et al., 2012; Péron et al., 2013; van Tricht et al., 2010; Vicente et al., 2009), we decided to investigate further whether ratings for the nontarget emotions differed between groups. In these post hoc analyses for each type of stimulus and each emotion scale, we did indeed find that the subjective experiences of musically induced emotions in patients with or without STN DBS and HC were qualitatively different. In these analyses, we were able to distinguish between the impact of PD and the impact of STN DBS.

For the stimuli inducing *wonder* (stimuli that had been rated the highest on the wonder and joyful activation GEMS emotions in previous studies), we observed a significant interaction between group and scale. Post hoc tests highlighted several explanations for this interaction effect. First, the impact of PD was manifested in a significant interaction between the HC and PD-MO groups. Whereas there was a clear difference between the HC group's Joyful activation and Tension ratings for *wonder* stimuli, PD-MO patients' experiences of Tension and Joyful activation were of similar intensity. Second, we were able to characterize the impact of DBS, as PD-DBS and PD-MO patients exhibited another interaction effect for their ratings of Tension and Nostalgia, with the PD-DBS group experiencing more Nostalgia and less Tension in response to the *wonder* stimuli than the PD-MO group did. Third, HC and PD-DBS patients differed on their evaluations

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of Joyful activation and Nostalgia, with the PD-DBS group rating the *wonder* stimuli as more nostalgic and less joyful than the HC did. These results suggest that, compared with HC, the patients with PD had more negative or mixed feelings towards music that was supposed to induce quite positive emotions, with PD-DBS patients rating the stimuli as more nostalgic, and PD-MO patients rating them as slightly more tension inducing. Similar results were found in a previous study of bipolar patients, featuring a very similar paradigm and the same stimuli (Choppin et al., 2016). In this study, music evaluated as inducing wonder was rated higher on negative emotion scales, notably tension and sadness, by bipolar patients in a euthymic state than by HC. This was interpreted as reflecting a residual tendency towards a negativity bias among bipolar patients, even when they were in an euthymic state.

To further investigate whether the results obtained in the present study could represent a negativity bias among patients with PD, we analysed the data for each separate emotion scale, to see whether any group experienced and evaluated a musical emotion differently from the others across the four types of stimulus. Analysis of the interaction effects only showed a trend towards significance for the scale quantifying Nostalgia, an emotion of medium valence and low arousal. Post hoc tests showed that this interaction was driven by a significant difference between the HC and PD-DBS groups on the target emotions of *melancholy* and w*onder*, in that HC evaluated the stimuli intended to induce *melancholy* as more nostalgic and the stimuli inducing *wonder* as less nostalgic than the PD-DBS patients did. This result disproved the interpretation that patients in the PD-DBS group had a bias for Nostalgia, as they were shown here to have rated the *melancholy* stimuli as less nostalgic than the HC did. This means that PD-DBS patients' rating of Nostalgia differentiated less accurately between the excerpts inducing *wonder* and *melancholy* than those of the HC group did. Taken together, the results of these two analyses suggest that the patients in the PD-DBS group confused positive and negative emotions, as they seemed to differentiate less well between stimuli that are usually evaluated as melancholic and those that normally induce emotions like wonder and joy, when it came to rating their ability to induce nostalgia. Compared with HC, patients under the influence of STN DBS seemed to overestimate the *bittersweetness* that is often associated with

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nostalgia, for stimuli supposed to evoke happy and enchanting feelings. Then again, they experienced this bittersweetness less with stimuli supposed to induce melancholy.

Our results therefore suggest that patients in the PD-MO group were slightly biased towards experiencing more Tension than HC, when exposed to music that was supposed to induce happy feelings (i.e., *wonder* stimuli, rated highly on the GEMS emotions Wonder and Joy), and DBS seemed to alter this effect, such that patients undergoing STN DBS no longer exhibited this bias in response to happy feelings. However, DBS seemed to reduce the ability to discriminate between the experiences of different musical emotions, particularly regarding the experience of Nostalgia, a complex emotional experience. Stimuli that normally induce *wonder* and *melancholy* evoked similar levels of Nostalgia in patients undergoing STN DBS. These patients therefore appeared to have a reduced ability to discriminate between the experiences of certain types of emotion, which can be regarded as an effect of *emotion blending*. Moreover, this corroborates a finding of the study by Vicente and colleagues (2009), who found that STN DBS lowered the level of differentiation between target and nontarget feelings induced by emotional film extracts. This was particularly true for negatively valenced emotions, namely sadness and fear. Similarly, Ory and colleagues (2015) found that feelings of disgust induced by film extracts were less intense after STN DBS. However, the emotion blending we observed in our study did not concern negative emotions per se, and could instead be interpreted as having an equalizing effect on emotions of different qualities, in particular *wonder* and *melancholy*. Interestingly, these two emotions represent quite complex emotional experiences, whereas the other two emotions we tested (*tension* and *power*) can be regarded as more basic emotions.

To our knowledge, the present study is the first to have investigated the experience of complex musical emotions in patients with PD. Studies exploring the ability of these patients to recognize emotions expressed by music have reported mixed results (Lima et al., 2013; Saenz et al., 2013; van Tricht et al., 2010). Some have found that it is mostly the recognition of negative emotions such as fear and anger that is impaired in patients, compared with healthy controls (Saenz et al., 2013; van Tricht et al., 2010). In our study, where we investigated the experience of musical emotions, we found that patients with PD who were not undergoing DBS differed from HC in their assessment of happiness-

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inducing stimuli. The fact that our results are not entirely congruent with previous studies of emotion recognition is not surprising, given the considerable difference between the actual experience and the cognitive recognition of an emotion. In particular, we observed that patients in the PD-MO group had more intense experiences of Tension and less intense experiences of Joy in response to music that usually evokes positive feelings such as joy and wonder in healthy participants. Tension, an emotion of high arousal and low valence, is the only clearly negative emotion in the GEMS. Therefore, it could be that the *wonder* musical excerpts simultaneously evoked negative emotions and a high level of arousal in the PD-MO patients. Moreover, tension is an emotion that can be regarded as being related to the basic emotion of fear, among others. In this respect, our results corroborate - albeit partly - results for emotion recognition in music (Lima et al., 2013; van Tricht et al., 2010), as it seems that the experience of happy, as well as tense or fearful feelings, with music is altered in patients with PD.

In PD, the dopaminergic circuits in the basal ganglia gradually become impaired. Moreover, it has been shown in the neuroimaging literature on musical emotions in healthy listeners that the basal ganglia, particularly their ventral part, play an important role in the processing of positive musical emotions (Koelsch, 2014; Salimpoor et al., 2011; Trost et al., 2012). It is therefore not surprising that patients with PD exhibit an altered experience of happiness. Given that it is a treatment for PD, STN DBS naturally has an impact on the dopaminergic circuits of the basal ganglia. What we found in the present study is that STN DBS seemed to normalize the altered experience of the negative emotion of tension in response to happy music, as patients in the PD-MO group exhibited a pronounced experience of this type of emotion, in comparison with the HC group, whereas those in the PD-DBS group did not. The musical emotion of Tension, which seemed to be altered in patients in the PD-MO group, has been shown to be processed in a network that includes the superior temporal gyrus, parahippocampal gyrus, precuneus, and premotor and motor areas, as well as the caudate nucleus of the basal ganglia (Trost et al., 2012). In PD, connectivity with the caudate nucleus may be impaired, resulting in an overestimation of the emotion of tension when the music is actually happy. For the musical emotion of Nostalgia, the ventral striatum has been shown to be involved in its processing, alongside the hippocampus and parahippocampus,

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anterior cingulate cortex, and OFC (Trost et al., 2012). As the STN is known to be closely connected to both the OFC and the ventral striatum, STN DBS may thus induce an alteration in the corresponding connectivity, consequently influencing the experience of pleasant music.

In conclusion, our study showed that patients with PD are able to experience musical emotions similarly to HC, whether or not they are undergoing STN DBS. However, we also observed that patients without STN DBS seemed to accentuate the emotional experience of Tension in response to happy music. In the patients with STN DBS, we instead observed an emotion blending effect, which equalized more complex musical emotions such as Wonder and Nostalgia.

Nevertheless, our study had several limitations. First, from a technical point of view, it could be argued that emotional disturbances under STN DBS could be due to aberrant electrode placements affecting the limbic loop. However, the dramatic improvement in motor symptoms and the concomitant reduction in the levodopa equivalent dose could be regarded as evidence that the electrodes were correctly placed in the motor regions of the STN. Nonetheless, given the small size of the STN in relation to that of the electrodes, even with well placed electrodes, there could be current diffusion to the limbic region of the STN, in which case the emotional consequences could be due to the STN stimulation. Second, as the experience of emotions, particularly musical emotions, is a highly subjective experience, musical emotions are especially challenging to study. Although individuals who did not like classical music were not invited to participate, our results may have been biased because the subjective experience induced by the stimuli was not strong enough for our samples. From this perspective, interindividual differences, such as personal music preferences or personality differences, may also have influenced the results. Third, our goal in investigating the experience of musical emotions in patients with PD and the impact of DBS was primarily to study the experience of more complex aesthetic emotions, such as musical emotions. However, owing to limitations on the duration of the study, we restricted the proposed stimulus types to the categories of *melancholy*, *wonder*, *tension* and *power*. Although the *melancholy* category encompasses emotions such as nostalgia, sadness, tenderness and peacefulness, it might have been interesting to study these more aesthetic and complex emotions individually.

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The present study therefore confirms the STN's involvement in the subjective experience of musical emotions. These aesthetic emotions allowed us to identify a much more subtle emotional consequence of STN DBS. Regarding future studies, it would be interesting to continue our research with a within-participants design, using the same patient group pre- and postoperatively, avoiding possible confounding factors, and provide anatomical-functional correlations based on FDG-PET imaging. This would be an interesting approach, as it would characterize the STN's contribution to the emergence of emotional experience and clarify its place in the neuronal networks responsible for this type of emotional processing. Moreover, emotional modifications due to STN DBS may have social consequences for patients with PD and a negative impact on their quality of life. Specifying the nature of these emotional modifications could also help to improve the DBS technique.

The experience of musical emotions in PD is an interesting field of study, particularly since there is increasing evidence that music can also be of therapeutic importance for patients (Raglio, 2015) - not only the well-known beneficial effects of its rhythm on gait and the initiation of movements, but also its emotional implications and benefits (Pacchetti et al., 2000). Therefore, more research in this domain is needed, featuring longitudinal study designs, in order to confirm our results, increase the understanding of the effects of DBS on affect, and establish music as a complementary tool in PD treatment and therapy.

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Highlights

- Emotional experiences in response to music are similar in HC, PD-MO and PD-DBS
- In PD patients the experience of tension in response to happy music is increased
- Patients with STN-DBS experience increased nostalgia in response to happy music
- STN-DBS induces a tendency of blurring boundaries between complex musical emotions

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