Effect of subthalamic deep brain stimulation on pain in Parkinson's disease

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ABSTRACT

Painful sensations are common in Parkinson's disease. In many patients, such sensations correspond to neuropathic pain and could be related to central alterations of pain processing. Subthalamic nuclei deep brain stimulation improves motor function in Parkinson's disease. Several structures of the basal ganglia are involved in nociceptive function, and deep brain stimulation could thus also modify pain perception in Parkinson's disease. To test this hypothesis, we compared subjective heat pain thresholds, in deep brain stimulation OFF and ON conditions in 2 groups of Parkinson's disease patients with or without neuropathic pain. We also compared pain-induced cerebral activations during experimental nociceptive stimulations using $H_2^{15}O$ positron emission tomography in both deep brain stimulation OFF and ON conditions. Correlation analyses were performed between clinical and neuroimaging results. Deep brain stimulation significantly increased subjective heat pain threshold (from 40.3 ± 4.2 to 41.6 ± 4.3, P = .03) and reduced pain-induced cerebral activity in the somatosensory cortex (BA 40) in patients with pain, whereas it had no effect in pain-free patients. There was a significant negative correlation in the deep brain stimulation OFF condition between pain threshold and pain-induced activity in the insula of patients who were pain free but not in those who had pain. There was a significant positive correlation between deep brain stimulation-induced changes in pain threshold and in pain-induced cerebral activations in the primary somatosensory cortex and insula of painful patients only. These results suggest that subthalamic nuclei deep brain stimulation raised pain thresholds in Parkinson's disease patients with pain and restored better functioning of the lateral discriminative pain system.

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1. Introduction

Patients with Parkinson's disease (PD) often suffer from non-motor symptoms. Several recent epidemiological studies have shown that 70% to 80% of PD patients experienced painful sensations [13,38]. Moreover, the prevalence of pain in PD is higher than in the general population [1,6]. Patients can experience different types of painful symptoms in PD, and several classifications have been proposed [18] with no definite consensus yet. Based on a physiopathological approach, 2 main different types of PD pains can be considered: nociceptive pain related to motor symptoms (dystonias, painful dyskinesias) as opposed to neuropathic pain

(classically described as burning, numbness, tingling) [4]. According to the International Association for the Study of Pain (IASP), neuropathic pain is caused by a lesion or a dysfunction of the somatosensory nervous system, and this is supported in PD by several studies showing abnormal pain thresholds [7,15,20,43], abnormal neuroimaging activations of nociceptive areas [7], and abnormal amplitude of nociceptive laser-evoked potentials [42,46].

High-frequency chronic deep brain stimulation (DBS) of the subthalamic nuclei (STN) is an efficient treatment for motor symptoms of advanced PD [30,32,33] modulating basal ganglia circuitry. As some structures of basal ganglia functional loops, such as striatum and thalamus, are also involved in pain processing, we hypothesized that STN-DBS could also modulate pain perception [9]. The effect of STN-DBS on pain in PD has only been partially evaluated. Few reports mentioned some clinical effect on pain [28,29,36]. Only 2 studies have explored the effect of STN-DBS on

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pain threshold in PD patients, and both had methodological limitations (ie, lack of double-blind and randomized assessments) [22,44]. Thus, the aim of the present study was to evaluate and compare the effect of high-frequency STN-DBS on subjective pain threshold in 2 groups of PD patients with or without central neuropathic pain.

We also investigated the effect of STN-DBS on pain-induced cerebral activity using positron emission tomography (PET) because our previous study showed an overactivation of nociceptive areas in PD patients during an experimental pain stimulation that might be modulated by STN-DBS [7].

2. Patients and methods

During a 6-month period, we proposed to all PD patients treated with STN-DBS and coming to the Neurology Department of Toulouse Hospital for a consultation to participate in this study. We finally included 16 patients (8 male and 8 female) with clinical diagnosis of PD according to the criteria of United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) [21,26] who were treated with STN-DBS for at least 3 months. Exclusion criteria were current depression (according to the DSM IV), cognitive impairment (Mini Mental State [MMS] <26) and treatment by neuroleptics. Eight PD patients were pain-free (without any acute and/or chronic pain or taking analgesic treatment). Eight patients experienced PD-related pain of the central neuropathic type. Because of the current lack of an international validated criteria or questionnaire of central neuropathic pain in PD, we used for that purpose, a clinical questionnaire developed by the Toulouse Hospital which is not yet validated but is based on a consensus between movement disorder and pain experts. This questionnaire consisted of 2 parts.

The first part of the questionnaire assessed possible causality between PD and pain based on the following 5 questions: 1) Did pain occur at PD onset, or was it influenced by motor condition? 2) Was pain influenced by dopaminergic medication(s)? 3) Was pain located in the hemibody most severely affected by PD? 4) Could any other etiology be identified? 5) Did the patient establish a link between pain and his/her disorder? Pain was considered as related to PD when 3 or more of these 5 items were positive.

The second part of the questionnaire provided a definition of central neuropathic pain based on 3 items: 1) pain should be defined such as tingling, burning, numbness, electric shocks, stabbing, painful cold (items from the patient's interview of the DN4 questionnaire [4]); 2) there should be no radicular systematization; and 3) pain should involve the hemibody most severely affected by PD. Central neuropathic pain was defined if at least 2 of these 3 items were positive (Table 1) This definition was closely related to central neuropathic pain described by Ford [17].

We investigated the effect of STN-DBS on pain using 2 different approaches in the same PD patients. The first approach was an open-label, long-term assessment comparing the scores of 2 clinical scales before and after STN-DBS surgery. This substudy was conducted in the 8 PD patients with central neuropathic pain only. These 2 scales were the Visual Analog Scale (VAS) for pain and the Neuropathic Pain Symptoms Inventory (NPSI) allowing discrimination of 5 dimensions of neuropathic pain (burning spontaneous pain, pressing spontaneous pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia) [5]. Patients were assessed before and at least 3 months after surgery.

The second approach was a short-term, randomized, controlled, cross-over trial. This part of the study was designed to be a double-blind approach, meaning that both the patient and the pain threshold evaluator were not aware about the STN-DBS condition OFF or ON, the STN-DBS being switched ON or OFF by an independent nurse who did not take part in the assessments. However, because of apparent motor effects of STN-DBS, the blinding may have been

compromised. All PD patients were evaluated after 12 hours of dopaminergic treatment withdrawal in 2 conditions: STN-DBS OFF, corresponding to a DBS interruption of 3 hours, and STN-DBS ON, while DBS was running for at least 3 hours using the usual stimulation parameters [45]. This substudy was conducted in the 8 pain-free PD patients and the 8 PD patients with central neuropathic pain. During each condition, the patients' motor status was assessed using the UPDRS motor score. For PD patients with central neuropathic pain, any analgesic treatment had to be stopped at least 24 hours before experimentation.

The primary efficacy parameter of the controlled substudy was the subjective heat pain threshold assessed using a Peltier-based contact temperature stimulation with a 12×25-mm contact thermode (MSA Thermotest, Somedic AB, Sweden) [19]. Pain threshold was measured on the thenar eminence of the most affected hemibody of PD patients using the method of levels [14] that did not take into account reaction time, which is often increased in PD patients in OFF condition. Initial temperature of the thermode of 30 °C was increased by steps of 3 °C. At the end of the stimulation lasting 30 seconds, patients were asked whether they felt pain or did not feel pain. After the first report of pain, the temperature of the next stimulus was diminished of 1.5 °C. The difference between subsequent stimuli continued to be halved down to a level of 0.2 °C.

The secondary outcome measure was pain-induced cerebral activity. We investigated cerebral activity with $H_2^{15}O$ positron emission tomography (PET) during nociceptive stimulation using an EXACT HR + scanner (CTI/Siemens, Knoxville, TN). After reconstruction, axial and in-plane resolution were 4.1 to 4.5 mm. Brain activity was monitored with an intravenous bolus injections of oxygen-15 radiolabeled water ($H_2^{15}O$) used as a regional cerebral blood flow (rCBF) tracer. Transmission scans were performed for the attenuation correction during image reconstruction. For all PET scans (in STN-DBS OFF and ON conditions), patients received 4 injections of 300 MBq of radiolabeled water to measure rCBF in 2 alternated and randomized conditions of heat stimulation: non-painful (NP; subjective pain threshold −5 °C) and painful (P) (subjective pain threshold plus 2 °C) experimental stimulations. Each thermal stimulation lasted 80 seconds (20 seconds before data acquisition and throughout the 60 remaining seconds).

Ethics committee approval was obtained, as well as written informed consent from each patient.

In the data analysis, clinical values were expressed as means ± standard deviation. In each group of PD patients, subjective heat pain threshold in STN-DBS OFF and STN-DBS ON conditions and clinical pain scores before and after DBS surgery were compared using a Wilcoxon test. Clinical characteristics and subjective pain thresholds were compared between the 2 groups of PD patients using a Mann–Whitney test. We also performed a correlation study between effects of STN-DBS on motor symptoms (difference in UPDRS III motor score between STN-DBS ON condition and STN-DBS OFF condition) and the effects of STN-DBS on pain threshold (difference in subjective heat pain threshold between STN-DBS ON condition and STN-DBS OFF condition) using a Spearman rank correlation test in each group of PD patients. The correlation coefficient ($R_{Spearman}$) and P values were calculated. Results were considered to be significant at $P < .05$.

Data analysis of PET scanning was performed using Statistical Parametric Mapping (SPM2) software (Wellcome Trust Centre for Neuroimaging, London, UK). We did not reorient our PET scan images before statistical analyses because of a possible right lateralization of cerebral mechanisms of pain processing suggested by several previous studies [7,10,23,24]. For each patient, PET scans were aligned with the intercommissural line using an average image, normalized into a stereotactic space and then smoothed with a 12-mm FWHM Gaussian filter.

Intragroups and intergroups analyses of rCBF were performed.