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Subthalamic Deep Brain Stimulation modulates proprioceptive integration in Parkinson's Disease during a postural task

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Highlights:

- **PD patients exhibit a deficit in the integration of proprioceptive information that affects postural control.**
- **STN-DBS improves the integration of proprioceptive information.**
- **By improving the integration of proprioceptive information, STN-DBS improves balance control**

Abstract:

Defective proprioceptive integration may play a role in the pathophysiology of motor symptoms in Parkinson's disease (PD). Dysfunction related to proprioceptively-evoked postural reactions in PD patients is still a controversial issue, with only a limited number of studies to date and mostly discordant results. The aims of the present study were 1) to determine whether or not the proprioceptive defect in PD underlies postural impairment and 2) whether or not deep brain stimulation of the subthalamic nucleus (STN-DBS) affects proprioceptive integration.

We examined proprioceptive integration during a postural task in 13 PD patients and 12 age-matched control subjects, using a muscle-tendon vibration paradigm.

Analysis of the center of pressure displacement and kinematic data indicates a greater degree of postural destabilization and a reduced ability to maintain a vertical orientation in PD. We found a significant positive effect of STN-DBS on these postural features.

Our findings indicate that Parkinson patients, even in the absence of any clinical evidence of instability, falls, or freezing, use proprioceptive information for postural control less efficiently than healthy subjects. Furthermore, STN-DBS was found to improve proprioceptive integration, with positive impacts on postural orientation and balance.

Abstract words count: 189

Introduction

Parkinson's disease (PD) is characterized by motor symptoms, including resting tremor, bradykinesia, rigidity, and postural impairment. Poor balance caused by impaired postural control is very disabling, increasing the risk of falls and hence reducing autonomy. Deficits in proprioceptive processing may be a major contributor to poor balance in PD. There is evidence that the integration of proprioceptive information for the perception of slow aiming movements is difficult for patients with PD (Klockgether et al., 1995). Impaired use of proprioceptive cues in PD has also been reported in studies of joint position sense, which established that PD patients have difficulties detecting or determining limb positions (Schneider et al., 1987; Klockgether et al., 1995; Demirci et al., 1997; Zia et al., 2000; Adamovich et al., 2001; Maschke et al., 2003; Byblow et al., 2003; Keijsers et al., 2005). Thus, perception of the body's position in space is impaired in patients with PD, which may at least in part explain their difficulty with achieving an upright and stable stance.

A direct link has been established between depressed proprioception and the postural instability problems encountered in individuals with PD. PD patients have been reported to have a reduced ability to stand on a moving platform compared to age-matched controls (Vaugoyeau et al., 2007) and to perform compensatory steps in response to surface translation (Jacobs & Horak, 2006) using mainly proprioceptive information. A number of studies have also reported greater body sway oscillation when ankle proprioception is perturbed through tendon vibration in PD patients, and this is particularly the case in severely impaired patients with clinical postural instability (Smiley-Oyen et al., 2006; Valkovic et al., 2006 a,b). This was interpreted as an inappropriate scaling of proprioception-triggered postural reactions and/or an inability to de-emphasize inaccurate/misleading proprioceptive information in the late stages of the disease. Yet, it remains necessary to elucidate whether proprioceptive integration for the regulation of body sway oscillations is fully intact in PD patients without postural instability and gait

difficulties. Furthermore, the vibrations in the above studies were not long enough (≤ 10 s) to get the individuals close to the limits of stability of the postural sway, thereby making the analyses less able (sensitive) to clarify how proprioception contributes to postural instability in PD. It has been shown that postural sway displacement and velocity are left unchecked by the control system until they exceed a certain systematic threshold above which balance becomes unstable (Collins & De Lucas, 1994; Delignières et al., 2011). Thus, it is best to study postural control near these limits. Following this line of thought, we examined whether the postural response to long duration (30 s) ankle muscle vibration was abnormal in patients who were still sensitive to dopa-therapy and without dopa-resistant axial motor symptoms (falls, freezing, or postural deformities) compared to age-matched controls.

Another important yet largely unexamined issue is the effect of subthalamic nucleus deep brain stimulation (STN-DBS) on the central processing of proprioceptive information and the related consequences on postural control. There is evidence that STN-DBS tends to improve proprioceptive acuity (Maschke et al., 2005; Shukla et al., 2013). However, although STN-DBS has been used for more than 20 years to improve motor fluctuations and dyskinesia in PD patients (Ashkan et al., 2004; Shapiro et al., 2007), it has modest effects on posture and balance (Bakker et al., 2004; Nilsson et al., 2005; Vrancken et al., 2005). A recent study has even suggested that balance improves during the first few months postoperatively, but that deterioration in postural control may occur one year postoperatively (Szlufik et al., 2018). Yet, regions of the basal ganglia (putamen/pallidum) are implicated in central processing of proprioceptive information (Goble et al., 2012) and STN-DBS induces major changes within the entire cortico-striato-pallido-thalamo-cortical system (Collomb-Clerc et al., 2015; Santaniello et al., 2015). Accordingly, we also examined the postural responses to tendon vibration when the patient's stimulation was turned off and on, to determine the influence of STN-DBS on the use of proprioception in postural control.

Materials and Methods

Subjects

Thirteen patients with PD without any clinical evidence of instability, falls, or freezing in the ON state (7 women, 6 men; median age: 62 ± 12 years; median disease duration: 12 ± 1 years) and 12 age-matched healthy subjects (HS) (6 women; 6 men, median age: 62 ± 12 years) participated in the study. There was no significant difference in terms of the ages of two groups of subjects ($U(13,12) = 67$; $p = 0.25$). The PD patients had undergone bilateral STN-DBS at least 6 months prior to the study (median: 12 ± 8 months). A full clinical examination of all of the patients was performed, and we excluded those with evidence of another significant neurological disease including peripheral nerve involvement. All of the subjects provided a signed written consent form that had been approved by the local ethics committee (CPP Sud Méditerranée 1). The clinical details of all of the patients are summarized in Table 1.

----- INSERT TABLE 1 HERE -----

Testing procedure

The experiment included two treatment conditions. In the first condition (OFFstim/OFFdopa), the stimulator was switched off at least 3 hours before the experiment after overnight withdrawal of their antiparkinsonian medication. In the second condition (ONstim/OFFdopa), the stimulator was switched ON at least 30 min before the experiment after overnight withdrawal of their antiparkinsonian medication.

Procedure

Two identical inertial vibrators were attached to the Achilles tendons of the subjects. The subjects were instructed to stand still and relaxed with their head facing forwards, hands at

their side, and feet in a natural position (10 cm apart). Each trial began with a 5 s baseline period, without vibration, followed by a 30 s period of vibration (frequency: 90 Hz, amplitude: 0.85 mm), and a final period of 25 s without vibration. The subjects performed 5 trials with their eyes closed.

Data collection/analysis

Reflective markers were placed on anatomical landmarks of the body, including the spinal process of the C7 vertebra, the sacrum, the mastoid processes, the acromions, the posterior superior iliac spines, the greater trochanters, the lateral tibial condyles, and the lateral malleolus. Centre of pressure (COP) coordinates and marker movements in the anteroposterior and medial-lateral directions were recorded using an AMTI force platform (400 Hz) interfaced with an ELITE motion capture system (100 Hz), respectively. The CoP displacement has been obtained from the ground reaction forces and moments, and only CoP displacement in the anteroposterior direction (i.e., CoPy) was kept for further analysis due to the fact that postural adjustments to tendon vibration mainly occur in the sagittal plane (e.g., Smiley-Oyen et al., 2002; Adamcova and Hlavacka, 2007; Caudron et al., 2010). The vertical inclination of the trunk was obtained from the angle formed between the line passing through the spinal process of the C7 vertebra and the sacrum and the vertical in the sagittal plane.

Vibration-evoked postural disturbances were subsequently evaluated using several dependent measures. The latency of the initial forward response and of the backward postural response to the vibration were derived from the CoPy displacement data. The amplitudes of the backward CoPy displacement and trunk inclination after 3 s and 30 s of vibration were also calculated relative to the 5 s baseline. The strategy for assessing backward sway at the beginning (i.e., 3 s) and end (i.e., 30 s) of the vibration was driven by the notion that the postural control system applies rather weak control over short sway displacements that intervene within the individual's limits of stability and tight control over long sway

displacements that approach or exceed these limits (Collins & De Lucas, 1994; Delignières et al., 2011). As such, the influence of proprioceptive manipulation on postural control may have differed depending on the time point at which the backward sway was assessed.

The above dependent measures were averaged over the 5 trials for each individual and treatment condition. Vibration-induced adjustments evaluated from the CoPy displacement provided information on postural stabilization, whereas the trunk inclination was more related to postural orientation (Amblard et al., 1985; Vaugoyeau et al., 2011). Moreover, the number of imbalanced trials in which backward steps occurred to prevent loss of balance was also considered as an additional dependent measure.

Statistical analysis

The statistical analysis was performed using Sigma-Stat software. Due to the small size of the group, non-parametric statistics were carried out. Mann-Whitney U tests and Friedman repeated measures analyses of variance were used to examine differences in dependent measures between groups and treatment conditions, respectively. Fisher's exact test was used to examine whether the proportion of trials including backward steps differed between the groups and between the treatment conditions. The threshold of statistical significance was set at $p < 0.05$.

Results

Postural response

Figure 1 shows the mean anteroposterior displacement of the center of pressure of the healthy subjects and of the parkinsonian patients with (ONstim/OFFdopa) and without (OFFstim/OFFdopa) treatment. Vibration applied to the Achilles tendons mainly induced displacement of the body in the backward direction in both the healthy subjects and the PD patients in all of the treatment conditions. Specifically, this postural response to Achilles

tendon vibration was similar to what was previously reported: an early forward shift of the CoP of small magnitude followed by a substantial backward displacement, which continues at stimulus offset before the CoP returns to its initial position. The plots point towards two main outcomes (see below for the statistical information). Group difference manifests at the end of the vibration only, with a further backward CoP displacement in the PD patients (OFFstim/OFFdopa condition) compared to the healthy subjects.

----- INSERT FIG.1 HERE -----

Imbalance

The results from the trials with imbalance are shown in Figure 2. Whereas no imbalance was observed in the HS, the PD patients were clearly imbalanced, with 39% of the trials including backward steps in the OFFstim/OFFdopa condition, and all of the patients having experienced at least one trial with imbalance. The Fisher's exact test revealed a significant difference between the PD patients and the HS ($p < 0.0001$).

STN-DBS significantly reduced the relative proportion of imbalanced trials in the PD patients (19% of the imbalanced trials in ONstim/OFFdopa; $p = 0.025$), although the performances of the PD patients never reached those of the HS ($p = 0.007$).

----- INSERT FIG.2 HERE -----

Temporal characteristics of the postural response

The statistical analysis revealed no disease and no STN-DBS effect on the temporal parameters, neither for the latency of the initial postural reaction nor for the latency of the backward postural reaction (Fig. 3A and 3B).

----- INSERT FIG.3 HERE -----

Spatial characteristics of the postural response

Centre of pressure displacement

After 3 s of vibration, there was no difference between the groups (Fig. 4A). **After 30 s of vibration**, the amplitude of the backward CoP displacement was greater in the PD patients in the OFFstim/OFFdopa state than in the HS ($U(13,12) = 17$; $p < 0.001$; Fig. 4B); it decreased when the stimulator was switched ON but remained significantly greater than in the controls ($U(13,12) = 40$; $p < 0.05$).

----- INSERT FIG.4 HERE -----

Trunk inclination

After 3 s of vibration, there was no significant difference between the groups (Fig. 5A). **After 30 s of vibration**, we found that the trunk inclination was significantly higher in the PD patients in the OFFstim/OFFdopa state compared to the HS (4° and 1.2° , for the OFFstim/OFFdopa PD patients and the HS, respectively; $U(13,12) = 18$; $p < 0.01$). STN-DBS induced a significant decrease of trunk inclination ($Z = -64$; $p < 0.01$), with the performances of the PD patients reaching those of the HS (1.4° and 1.2° for the ONstim/OFFdopa PD patients and the HS, respectively) (Fig. 5B).

----- INSERT FIG.5 HERE -----

Discussion

Our results showed 1) a greater postural destabilization and a reduced postural orientation control in PD patients without treatment at the end of the vibrations, and 2) a significant positive effect of STN-DBS on these postural features and unbalance.

A proprioceptive defect in PD that impacts posture

After 30 s of vibration, the PD patients had a greater degree of postural destabilization and a greater backward trunk inclination compared to the healthy controls, and consequently maladapted and exaggerated responses to vibrations. This indicates that PD patients without any axial motor symptoms (Hoehn and Yahr ≤ 3 and ≤ 2 in the OFF and ON states, respectively) have impaired proprioceptive control of posture. This result agrees well with a number of previous studies that reported proprioceptive impairment in PD stemming from a reduced ability to determine limb position changes (Schneider et al., 1987; Klockgether et al., 1995; Demirci et al., 1997; Zia et al., 2000; Adamovich et al., 2001; Maschke et al., 2003; Byblow et al., 2003; Keijsers et al., 2005). Nevertheless, only a few studies to date have analyzed the contribution of proprioceptive afferents to postural control using tendon vibrations in PD, and they have brought mixed results. Some of these studies reported larger postural responses to the vibrations (Valkovic et al., 2006 a,b; Bekkers et al., 2015) while others showed no effect of the vibrations (Smiley-Oyen et al., 2002.). A closer look to these results reveals that proprioception affected postural control essentially in patients with clinically significant postural instability (Valkovic et al., 2006 a,b). Accordingly, our study shows for the first time that patients without dopa-resistant axial motor impairment have difficulties in proprioceptive postural control. Furthermore, it is also important to interpret this result given the duration characteristics of the vibration that assessed position and motion sense of the proprioceptive system. Indeed, proprioception encompasses both the perception of the position of the joints and the perception of joint movements and more specifically the speed of movement (Gandevia et al., 2002; Goble et al., 2009, Proschke and Gandevia, 2013). Concerning postural control, the integration of position and motion feedback information is critical to accurately estimate body position and velocity and then to generate appropriate motor responses to stabilize vertical posture (Kiemel et al., 2002; Jeka et al., 2004). In this context, a short duration of stimulation evaluates more the ability to monitor the speed of the

backward sway movements rather than a change in the body position. Conversely, disturbances in postural adjustments after 30 seconds of vibration, as reported here, may reflect a reduced ability to sense extreme sway positions, beyond which body orientation and stabilization are in jeopardy. Closely related, the long duration of the vibration may have brought the postural sway near to the individual's limits of stability, where it is easier to demonstrate any postural impairment due to tight control of sway displacement and velocity (Collins & De Lucas, 1994; Delignières et al., 2011). Nevertheless, there is evidence that PD does not only affect proprioception while standing but also the integration of multisensory information (Hwang et al., 2016). Hence, we cannot rule out that an impairment of multisensory reweighting in postural control may have also contributed to the exaggerated postural response to the vibration. PD patients would be less prone to neglect irrelevant proprioceptive information to the benefit of the other senses which are more adapted to the situation because they are less destabilizing, the otolithic information in our case.

STN-DBS improves proprioceptive functioning

The significant decreases of CoP and trunk displacements and of the unbalanced trials in the ONstim/OFFdopa condition revealed a positive impact of STN-DBS on postural control. The outcomes of previous studies that investigated the effect of STN-DBS on postural control are rather contradictory, which could be attributed to variations in the aspects of postural function under scrutiny (e.g., balance, anticipatory postural adjustments, body orientation). For example, it has been reported that the frequency of falls can increase after STN-DBS (Rocchi et al., 2002, 2004; Follett et al., 2010). On the other hand, STN-DBS may improve static postural control, but has no effect and sometimes even a deleterious effect on dynamic postural control. Therefore, our study adds further weight to the idea that STN-DBS has positive impact on postural control through influence on proprioception, and especially static

proprioception. It is however important to note that CoP displacement at the end of the vibration was still significantly greater in PD patients in the ONstim/OFFdopa state of treatment compared to healthy subjects. Hence, STN-DBS did not completely normalize the postural reaction to the vibration.

This improvement of postural control suggests that STN-DBS improves proprioceptive integration. Although there have only been a few studies to date that directly examined the effects of STN-DBS on proprioception, similar positive effects of STN-DBS on proprioceptive function have been described. Maschke et al. (2005) found that STN-DBS produced a small but significant improvement in proprioceptive acuity in a task of passive forearm displacement detection. Moreover, it has been demonstrated that STN-DBS can improve the accuracy of limb localization in 3D space (Lee et al. 2013). Interestingly, studies investigating pain perception have shown that STN-DBS mainly influenced the detection thresholds (Cury et al., 2016 a,b). These authors suggested that these changes could depend on the specific effects of STN-DBS on somatosensory loops. Aman et al. (2014) have demonstrated that STN-DBS also improves tactile perception, providing further evidence that STN-DBS-related improvements are not due to motor function improvements alone but also enhanced somatosensory processing.

The modulation of the proprioceptive function by STN-DBS is sound given previous neurophysiological and neuroimaging studies. It is well known that STN-DBS induces major changes within the entire cortico-striato-pallido-thalamo-cortical system (Collomb-Clerc et al., 2015; Santaniello et al., 2015). Several fMRI studies, using the tendon vibration paradigm, have shown that proprioceptive processing involves cortical (including parietal, motor, and sensorimotor areas) and subcortical structures (including the basal ganglia) (Goble et al., 2011 and 2012; Cignetti et al., 2014). In elderly people, Goble et al. (2012) found that reduced activation of the putamen correlated with a decline in the static proprioceptive performance.

Furthermore, by using transcranial magnetic stimulation in implanted PD patients, it has been demonstrated that STN-DBS influences non-dopaminergic pathways involved in sensorimotor integration (Sailer et al., 2007). Use of the local field potential during passive movements and peripheral somatosensory stimulation has demonstrated that STN is involved in somatosensory processing (Trenado et al., 2017).

Although our findings confirm previous conclusions that STN-DBS can mediate proprioception, we should, however, mention a potentially important limitation. Indeed, since the effect of STN-DBS was analyzed in the same way for all of the patients, i.e., STN-DBS OFF followed by STN-DBS ON, one cannot exclude the possibility that the improved performances of PD patients in the ONstim/OFFdopa state of treatment were related to adaptation of the subjects to tendon vibrations. Such an adaptation has been reported in previous studies that used repetition of Achilles tendon vibration during free standing (Fransson et al. 2002; Smiley-Oyen et al. 2002; Caudron et al. 2008). However, the fact that we did not observe any difference between the performance of PD patients in the OFFstim/OFFdopa and the ONstim/OFFdopa after 3 seconds of stimulation suggests that the improvement in postural performance at the end of the vibration was related to an effect of STN-DBS and not to adaptation of the central nervous system to tendon vibrations.

In conclusion, our study provides new evidence that impairment of proprioceptive functioning impacts directly on postural control in PD. More specifically, we have shown that PD patients without axial motor symptoms inadequately integrate proprioceptive information, thereby leading to deleterious effects on postural orientation and balance control. We also hypothesize that the proprioceptive integration deficit in PD may affect static more than dynamic proprioceptive information early on in the course of the disease. Furthermore, STN-DBS was found to improve proprioceptively-evoked postural control, although partially. That leaves

room for other therapeutic tools to further improve proprioceptive integration and reduce postural disturbances in PD.

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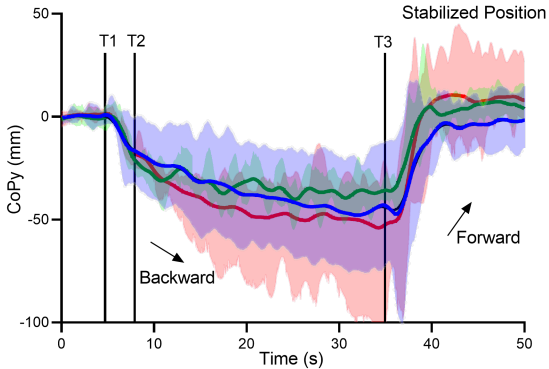
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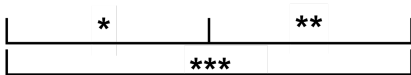
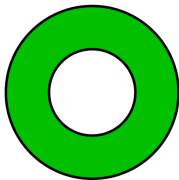
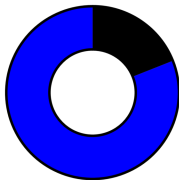
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



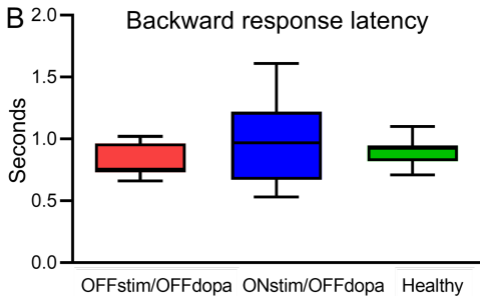
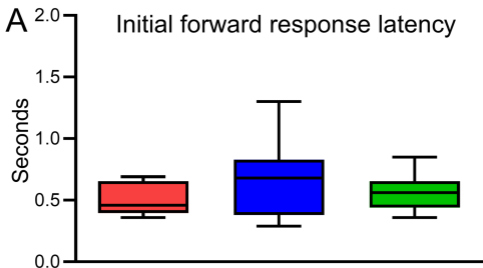
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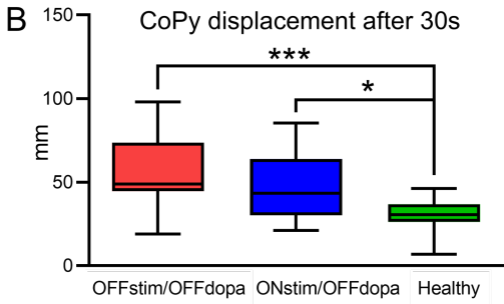
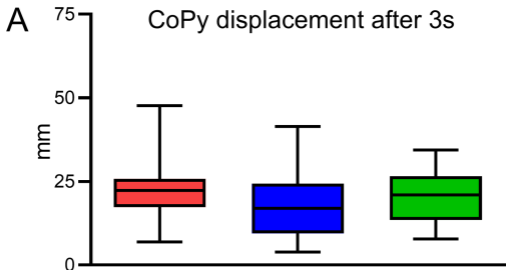
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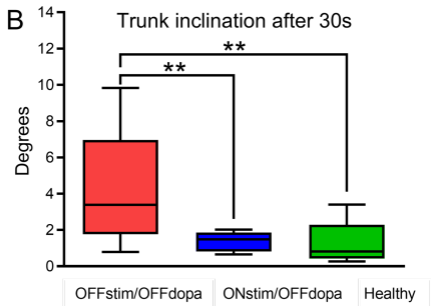
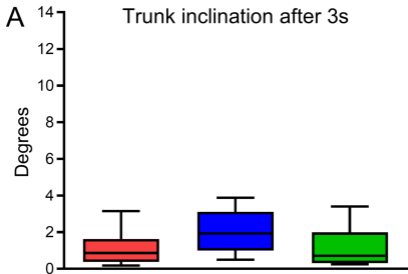
Healthy



 % of Imbalanced trials  % of Balanced trials







Patient	Age (years)	Disease duration (years)	Months after surgery	Hoehn and Yahr score		UPDRS (part III) score		% of UPDRS Part III improvement
				OFF	ON	OFF/OFF	ON/OFF	
P1	56	11	6	3	2,5	23	7	70
P2	58	9	13	3	2,5	38	14	63
P3	69	13	6	2	2	21	4	81
P4	66	19	15	3	2,5	35	18	49
P5	66	13	36	3	2,5	46	13	72
P6	62	15	14	3	1,5	35	16	54
P7	57	13	6	2,5	2	18	5	72
P8	71	8	6	2	2	16	4	75
P9	55	9	12	2	2	57	13	77
P10	55	11	6	2	2	29	12	59
P11	70	12	24	3	2	48	16	67
P12	69	16	12	3	2	37	10	73
P13	60	12	14	3	2,5	36	14	61
Median	62	12	12	3	2	35	13	70
IQR	57-69	11-13	6-14	2-3	2-2.5	23-38	7-14	61-73