Correlation between deep brain stimulation effects on freezing of gait and audio-spinal reflex

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Highlights:

- Audio-spinal reflex is increased by STN DBS in PD patients, irrespective of drug therapy.

- There in an inverse correlation between this increase and burden of FOG in PD patients.

- Audio-spinal reflex might be used to assess different stimulation strategies aimed at reducing FOG.

Abstract:

Objective: A network of cortical, subcortical and brainstem structures might be involved in freezing of gait (FOG). Subthalamic nucleus (STN) deep brain stimulation (DBS) could modulate this network. The audio-spinal reflex (ASR), reduced in PD, but increased by treatment, can be used to further investigate that locomotor network. The aim of this study is to find whether a correlation exists between ASR and FOG in PD patients under DBS.

Methods. In 14 PD patients with STN DBS and previous FOG, ASR was recorded, with DBS switched on and off. We also assessed FOG Questionnaire (FOGQ) and Unified Parkinson's Disease Rating Scale (UPDRS) Part III.

Results. Switching "on" DBS increased ASR amplitude (+ 33.2% with DBS ON, $p = 0.048$). We also found a significant inverse correlation between FOGQ and modulation of ASR by DBS ($r = -0.59$, $r^2 = 0.35$, $p < 0.05$).

Conclusions. This study shows that the incremental effect of DBS on ASR is greater in PD patients with less severe FOG.

Significance. This study shows a link between electrophysiological and clinical data about gait control. It might contribute to better understand why some DBS patients report heavy FOG and others do not. ASR might be used to evaluate or maybe predict the effect of stimulation parameters changes on FOG.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder with progressive motor impairment, accompanied by non-motor symptoms. Besides the classical triad (rest tremor, rigidity and akinesia), gait disorders such as freezing of gait (FOG) or imbalance greatly contribute to disability (Perez-Lloret *et al.*, 2014). FOG consists of a lack or a marked reduction of feet progression despite the intent to walk. It may be relieved by dopaminergic drugs, and is then named "off FOG". It may also be unresponsive to levodopa and even in some cases induced by treatment ("on FOG") (Bloem *et al.*, 2004; Espay *et al.*, 2012; Heremans *et al.*, 2013; Nantel and Bronte-Stewart, 2014; Nutt *et al.*, 2011). Pathophysiology of FOG remains uncertain, and numerous hypotheses have been risen. Reviews (Nieuwboer and Giladi, 2013; Nutt *et al.*, 2011) focused on pathophysiology of this phenomenon highlight the complexity of the mechanisms implied.

Subthalamic nucleus (STN) deep brain stimulation (DBS) can be considered when pharmacological treatment no longer provides enough relief of symptoms; DBS improves tremor and limb akinesia and rigidity (Deuschl *et al.*, 2006; Fasano *et al.*, 2010, 2012; Krack *et al.*, 2003; Schuepbach *et al.*, 2013). Patients usually describe an improvement of their condition (Vercruysse *et al.*, 2014), but gait and posture impairment tend to worsen over time, probably because of spreading neurodegeneration, involving cortical structures and brainstem nuclei such as pedunculopontine nucleus (PPN) (Devos *et al.*, 2010; Fasano *et al.*, 2010; Hirsch *et al.*, 1987; Krack *et al.*, 2003). Lower frequency (60Hz) stimulation has been reported to relieve FOG in some cases (Xie *et al.*, 2015). PPN stimulation has also been proposed, since it might be involved in locomotion disturbances (Benarroch, 2013; Ferraye *et al.*, 2008; Fraix *et al.*, 2013; Lau *et al.*, 2015; Pahapill and Lozano, 2000; Tattersall *et al.*, 2014).

Those structures are part of a network involved in locomotion, the connectivity of which seems modified in PD with FOG (Fling *et al.*, 2013, 2014). PPN is known to have outputs on nuclei of reticular formation, and, among those, on nucleus reticularis pontis caudalis (NRPC), also named caudal pontine reticular formation (Homma *et al.*, 2002). This nucleus is implied in an electrophysiological reflex, the audio-spinal reflex (ASR) (Davis, Gendelman, *et al.*, 1982; Davis, Parisi, *et al.*, 1982; Leitner *et al.*, 1980). ASR is similar to startle reaction. It consists of facilitation of soleus' H-reflex after hearing a brief, loud and sudden sound (Rossignol and Jones, 1976; Rudell and Eberle, 1985). It is easy to record and quantify and is

present in all subjects with measurable H-reflex, in contrast to startle reaction (Delwaide and Schepens, 1995). It had been shown previously that ASR amplitude was decreased in PD patients compared to healthy controls, and that this reduction was corrected by levodopa (Delwaide *et al.*, 1993). ASR is also increased by STN DBS (Pötter *et al.*, 2008). ASR might then be studied in PD patients with STN DBS as an indirect marker of PPN function.

If NRPC and PPN are connected, then some relationship may exist between FOG severity and ASR modifications resulting from STN stimulation. Such a correlation between the ASR and quality of gait has not been searched so far. If such a relationship exists, ASR study might be useful to detect PD patients whose FOG would be likely to respond to DBS.

2. Methods

2.1. Population

Table 1 shows our population's characteristics.

	PD patients	Healthy controls
Number of patients	14	9
Age (yrs.) (median and extremes)	58.5 (49-73)	57 (50-74)
Men/Women	11/3	5/4
Levodopa equivalent daily dose (mg/d) (mean and SD)	544.9 +/- 407.2	NA
UPDRS (DBS ON) (mean and SD)	22.6 +/- 10.7	NA
UPDRS (DBS OFF) (mean and SD)	46.5 +/- 18.4	NA
Disease duration (years) (mean and SD)	12.9 +/- 3.9	NA

All patients and control subjects were informed in details of the study design approved by local Ethics committee, and gave oral and written consent. We initially recruited ten healthy subjects, free from neurologic diseases such as cerebrovascular disease, dementia, movement disorders, and peripheral neuropathy. They received no medication with central nervous system effect, such as anti-epileptic drugs, benzodiazepines, anti-depressants, etc. One healthy subject did not complete the protocol because of discomfort due to electrical stimulation. We could thus record nine controls.

We recruited twenty patients diagnosed with idiopathic PD according to UK brain bank criteria (Hughes et al., 1992) and EFNS/MDS-ES guidelines (Berardelli et al., 2013) who had undergone bilateral implantation of electrodes (Medtronic°DBS Lead model 3389) in STN. All patients had complained about FOG phenomenon during disease course, at least once a month. Deep brain stimulation surgery was performed either in the Centre Hospitalier Régional de Liège, Citadelle, or in the Centre Hospitalier Universitaire de Liège, Sart Tilman. In both centers, patients had a pre-operative MRI. Electrodes placement was based upon stereotactic measurements, micro-electrode recordings and intra-operative clinical assessment. Eligibility criteria for surgery were motor fluctuations, levodopa responsiveness and preserved cognitive and mood functions (Bronstein et al., 2011). Drug therapy remained stable throughout the study. One PD patient did not tolerate the OFF stimulation condition. Two patients withdrew after initial consent. One patient had a concomitant severe disease. One patient had transport difficulties. One patient, whose values of direct motor responses (M-waves) to tibial nerve stimulation were too variable, was excluded from the analyses, thus leaving fourteen patients for the full protocol.

There were no significant differences between healthy subjects and PD patients, in terms of age and sex (Mann-Whitney U-test: $U = 51.5$, $p = 0.47$ and $U = 48.5$, $p = 0.36$).

PD patients were assessed with Unified Parkinson's Disease Rating Scale (UPDRS) part III (Fahn et al., 1987), immediately before the examination. They were also administered a FOG Questionnaire (FOGQ), designed to evaluate freezing of gait severity (Giladi et al., 2009). The ASR was recorded twice in PD patients: with DBS switched on and off. The order of conditions ON and OFF was randomly ascribed. When DBS was set off, at least 1h elapsed before assessing UPDRS III and recording ASR.

2.2. Data acquisition

2.2.1. Experimental procedure

Experiments were conducted using the Signal 4.10® software (Cambridge Electronic Design, CED, Cambridge, UK). Outputs from the computer were transmitted to a data acquisition unit (Micro1401, CED). These outputs were used to produce the sound, and to trigger the nerve stimulator (Digitimer DS7A, Welwyn Garden City, UK). Compound muscle action potentials were amplified through a CED 1902 amplifier, and transmitted to the Micro1401 unit, then analyzed by the Signal software.

2.2.2. Baseline H-reflex detection

Patients sat on an armchair, in a relaxed position, with the recorded leg fixed so that knee and ankle were flexed with an angle of about 100° and 90°, respectively. The study was performed on one leg based upon the absence of scar or any surgery. It has been shown before that ASR is the same bilaterally both in normal and parkinsonian subjects, whatever side is predominantly affected by the disease (Delwaide *et al.*, 1993). If tremor was present, the less affected side was chosen in order to avoid interference of tremor with recordings. H-reflex was detected by surface electrodes on the soleus muscle. Active electrode was placed above soleus muscle, and reference electrode above Achilles' tendon. Distance between both electrodes was about 80mm. Ground electrode was placed on tibial crest. Tibialis nerve was stimulated by a square electric pulse of 1ms, delivered in popliteal fossa with a bipolar electrode. Tibial nerve stimulation intensity was individually adjusted. Amplitude of H-reflex was recorded by peak to peak sum of the signals from 25ms to 60ms after nerve stimulation. Popliteal stimulation intensity was gradually increased until we obtained an electric activity with shape and delay concordant with an H-reflex. From this liminary stimulation, ten steps of 0.5mA were made. Five measurements of H-reflex's amplitude were recorded for each step. We then obtained a graph with the mean H-reflex amplitude for each stimulation intensity. This allowed to set stimulation intensity yielding an H-reflex around 50% of its maximum. It has been shown before that H-reflex amplitude is more modulable with such an intensity (or at the stimulation producing 15% of the maximum soleus' motor response (Delwaide *et al.*, 1993). ASR was recorded with this intensity. In all subjects, a small M response was elicited to check stability of H-reflex and ensure that no displacement of stimulating electrodes might hamper the stability of response.

2.2.3. Audio-spinal reflex

ASR was elicited by a sudden and brief sound, provided through an audio headset and produced by a 20ms train of electric pulses. The sound produced had a frequency of 2500Hz and an intensity of 85dB.

The sound was followed by stimulation of tibialis nerve, and recording of H-reflex. Stimulations were performed with delays of 25, 50, 75, 100, 125, 150, 175, 200, 225, 250 or 275ms after the sound. We recorded five trials in each condition. Five stimulations were performed without any sound, in order to collect baseline H-reflex. Conditions were randomly set, as well as intervals between nerve stimulations, with a median interval of 15s.

In each subject, we reviewed M-waves. Recordings were discarded if artefacts or M-waves variation were present.

2.2.4. Curves alignment

The ASR occurs between 75 and 150ms after the auditory stimulus, and since central conduction time may present inter-individual differences, the highest mean value of H-reflex was chosen as optimal conditioning-test interval, between delays of 100ms, 125ms and 150ms for each subject, and a shift of all values was then performed so that maxima were aligned (peak audio-spinal reflex). In four subjects (one patient and three healthy subjects), we recorded at least two sessions, in the same state (ON) for the patient. In these subjects, the highest mean H-reflex value occurred at the same conditioning-test interval in both sessions (data not shown). Furthermore, in PD patients, the highest unconditioned H-reflex amplitudes were comparable in both conditions (ON and OFF DBS).

In order to compare subjects, all values recorded in mV were divided by the subject's mean H-reflex without ASR, calculated from five different trials. These values were expressed in percentage. A mean value for each conditioning-test interval (25ms, 50ms, 75ms, 100ms, etc.) was thereafter calculated for each subject.

2.3. Statistical analysis

Statistical analysis was performed through Statistica 12® (Statsoft, Paris, France). We performed a paired-sample Wilcoxon test on mean value of baseline H-reflex amplitude stimulus and H-reflex at peak of ASR, in order to confirm previously published results in healthy subjects (Rossignol and Jones, 1976; Rudell and Eberle, 1985).

In PD patients, we performed a paired-sample Wilcoxon test on mean value of H-reflex at peak ASR, in ON and OFF conditions. We also calculated the difference between H-reflex amplitude at ASR peak, in "ON and OFF DBS" conditions (namely, DBS effect on ASR amplitude = H-reflex at ASR peak ON stimulation – H-reflex at audio-spinal reflex peak OFF stimulation).

We performed a correlation analysis (Pearson's r) between DBS effect on ASR and FOG questionnaire score "ON". Correlations between DBS effect on ASR and DBS effect on UPDRS, and UPDRS and disease duration and levodopa equivalent daily dose (LEDD) (Tomlinson *et al.*, 2010) were also tested.

3. Results

3.1. Clinical data

Mean disease duration of PD patients was 12.9 ± 3.9 years (extremes: 6-23 years). Under unchanged medical treatment, mean UPDRS with DBS switched ON and OFF was 22.6 ± 10.7 and 46.5 ± 18.4 respectively. This difference was statistically significant ($Z = 3.30$, $p = 0.001$). LEDD ranged from 0mg/day to 1179.5mg/day (mean = 544.9 ± 407.2). LEDD was negatively correlated with the UPDRS OFF score ($r = -0.64$, $r^2 = 0.41$, $p = 0.014$) and UPDRS ON score ($r = -0.55$, $r^2 = 0.30$, $p = 0.043$). Change in UPDRS score (UPDRS OFF – UPDRS ON) was also negatively correlated with the LEDD ($r = -0.57$, $r^2 = 0.32$, $p = 0.035$). There was no significant correlation between FOG questionnaire and UPDRS or disease duration.

3.2. Audio-spinal reflex

Figure 1 shows the curves of the audio-spinal reflex obtained in healthy subjects and in PD patient, with DBS switched ON and OFF. As explained above, ASR is expressed in percentage of baseline H-reflex, in order to compare individuals, without interference of muscle mass or skin thickness. ASR curves from individual subjects were shifted so that peaks were aligned (see methods). Mean (± SD) times to peak were 119.4ms (± 20.8ms) for healthy subjects, 114.3ms (± 18.9ms) for PD patients and 116.3ms (± 19.4ms) for the whole population.

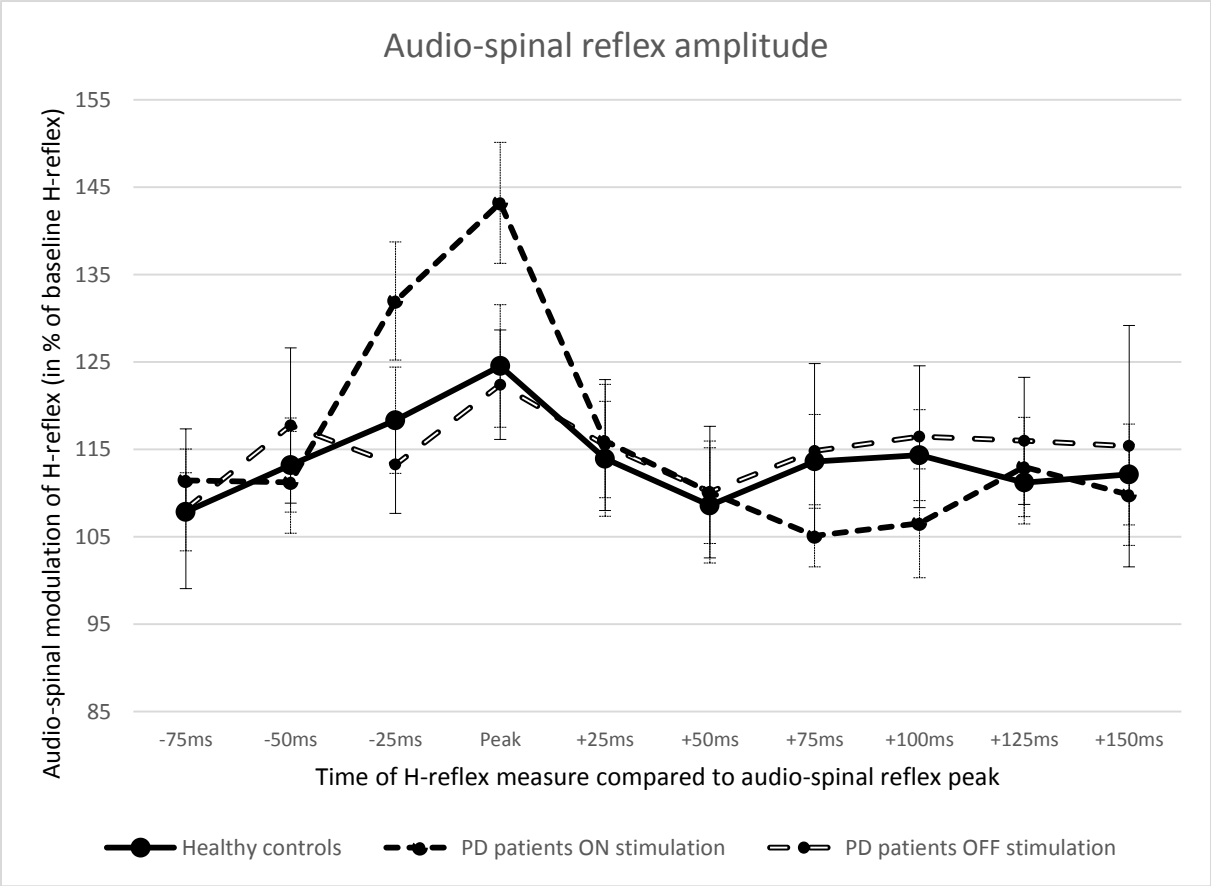

Figure 1: Audio-spinal reflex in healthy controls, PD patients ON stimulation and ON medication and PD patients OFF stimulation and ON medication, with standard errors.

The modulation of H-reflex by ASR resulted in a significant increase of +17.8% ($p = 0.0077$, $Z = 2.67$) in healthy subjects, +14.3% ($p = 0.0023$, $Z = 3.04$) in PD patients OFF stimulation, and +47.5% ($p = 0.0015$, $Z = 3.17$) in PD patients ON stimulation. Since PD patients were still taking their usual antiparkinsonian medications, the presence of an ASR whose amplitude is not significantly different from the healthy subjects (post hoc analysis with Mann-Whitney U-test, $p > 0.05$) is in agreement with the known effect of dopaminergic agents on audio-spinal modulation of H-reflex (Delwaide *et al.*, 1993), even in the OFF stimulation condition.

In PD patients, a significant difference was shown between ASR amplitude in the two stimulation conditions (i.e. +33.2% ON vs OFF stimulation, $p = 0.048$, $Z = 1.98$; see Figure 2).

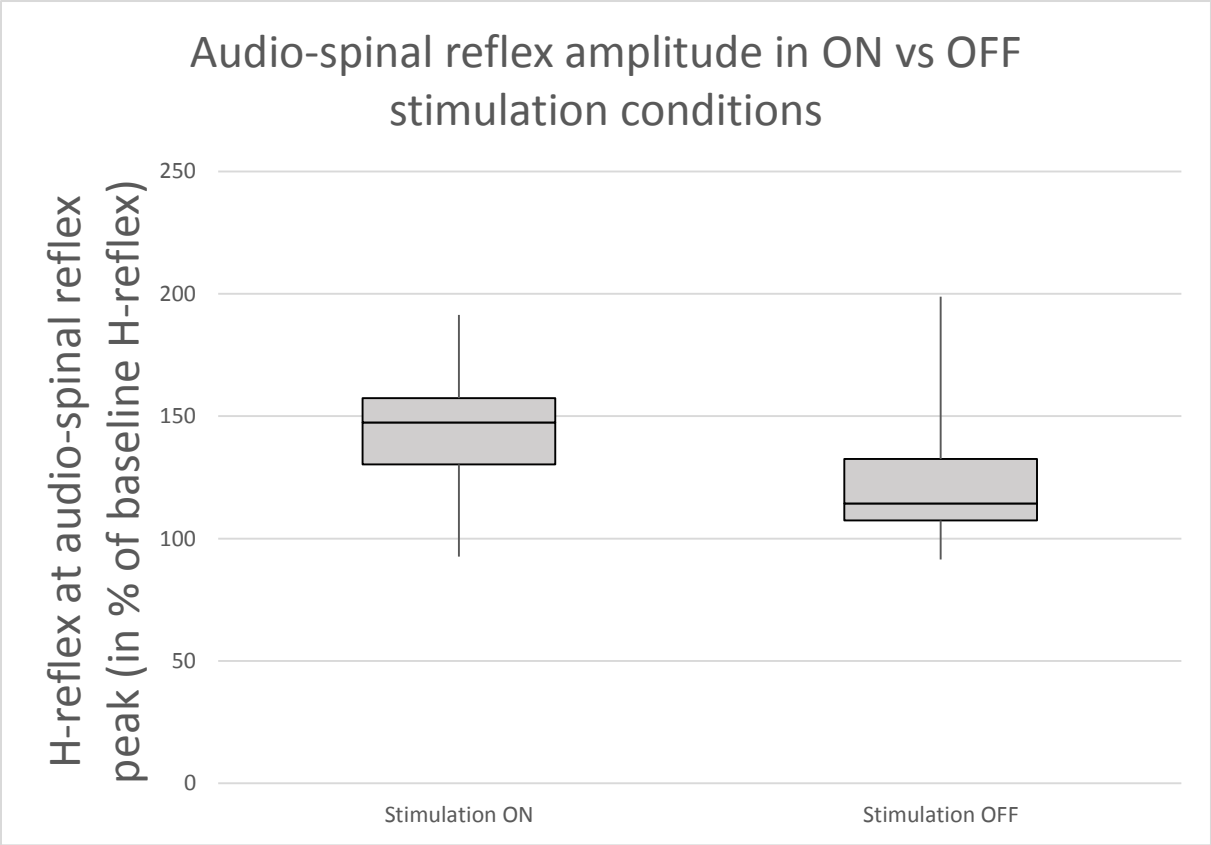

Figure 2: H-reflex amplitude at audio-spinal reflex peak, stimulation ON vs OFF, with medians, P25 and P75, minima and maxima.

3.3. Clinical and electrophysiological correlations

A significant inverse correlation was found between scores at the FOG questionnaire and DBS effect on ASR ($r = -0.59$, $r^2 = 0.35$, $p = 0.025$; see Figure 3). This implies that the incremental effect of STN DBS on ASR is greater in patients experiencing less FOG phenomena with combined pharmacological and surgical treatments. There was no correlation between DBS effect on ASR and its effect on UPDRS. There was no correlation either between LEDD or disease duration and DBS effect on ASR. A correlation was found between disease duration and the ASR amplitude in ON stimulation condition ($r = 0.58$, $r^2 = 0.34$, $p = 0.031$).

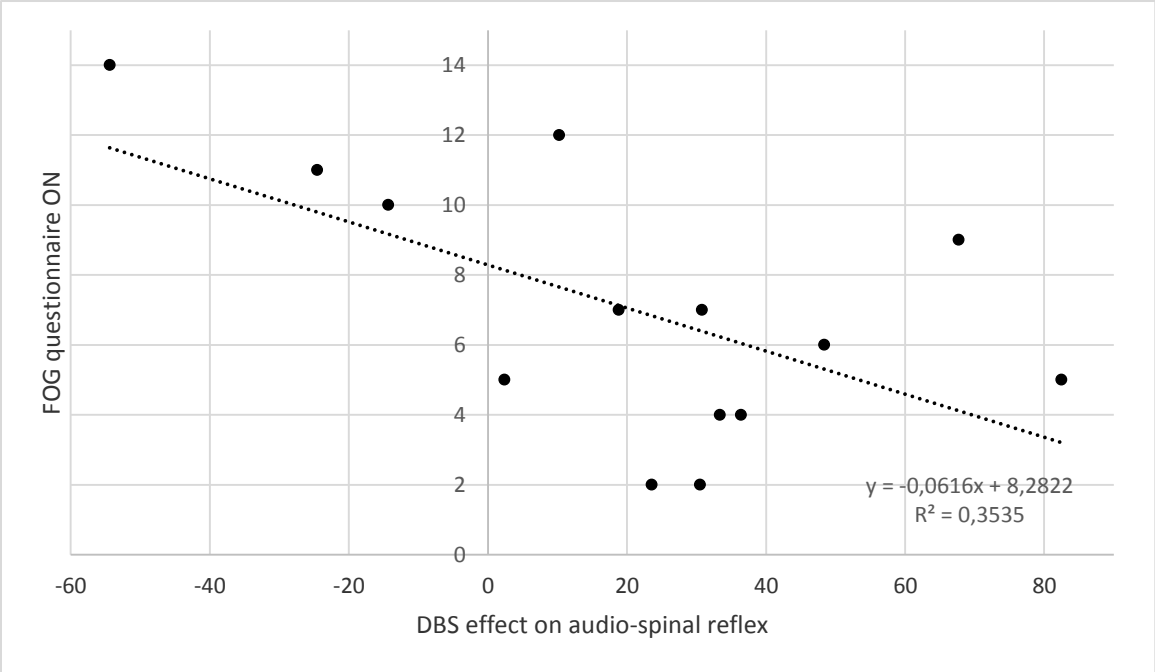

Figure 3: Correlation between DBS effect on audio-spinal reflex amplitude (=Audio-spinal reflex amplitude ON stimulation – audio-spinal reflex amplitude OFF stimulation) and FOG questionnaire score.

Analysis of variance did not show any significant effect of time to peak ASR on FOG questionnaire scores.

4. Discussion

4.1. Audio-spinal reflex and STN DBS

Our study first confirmed that ASR could be elicited in all healthy individuals with the chosen experimental setup. In pharmacologically treated PD patients, STN DBS increased this ASR, as already described in patients without pharmacologic treatment (Pötter *et al.*, 2008). STN DBS thus still increases ASR, even in PD patients treated with dopaminergic medications. As was shown in this previous study (Pötter *et al.*, 2008), ASR is higher in PD patients under STN DBS than in healthy subjects. The mechanism suggested by Pötter et al. – STN DBS reduces the inhibitory output from basal ganglia to PPN and NRPC – might explain this finding: NRPC would be released by DBS from inhibitory inputs beyond physiological threshold, thereby generating an increased ASR.

4.2. FOG and DBS effect on audio-spinal reflex

We showed a correlation between ASR and a clinical score assessing FOG: patients who had lower scores on FOGQ (meaning they had less frequent or less severe FOG episodes) had an higher increase in ASR amplitude under STN stimulation, whereas those who experienced

frequent and/or severe FOG episodes had a smaller increase of ASR, or even a decrease of this reflex. Such relationship could be suspected from an earlier electrophysiological study, which showed a reduced response to startling stimuli in PD patients with FOG (Nonnekes *et al.*, 2014). We compared the ON-stimulation FOG questionnaire to the DBS effect on ASR amplitude. Clearly, higher increase of ASR amplitude under STN DBS implies that the anatomical structures (reticular nuclei) underlying this reflex remain strongly modulated by STN DBS. This is less evident in patients with more severe FOG. This inverse correlation between DBS effects on ASR and FOG severity strongly suggest that both phenomena share common neural structures, presumably in reticular formation.

Some studies (Moreau *et al.*, 2008; Ricchi *et al.*, 2012; Sidiropoulos *et al.*, 2013) tried to evaluate the effect of a reduced stimulation frequency on axial symptoms. Improvement is generally transient. We might use the ASR to further investigate the effects of frequency of stimulation on brainstem structures, and maybe before deciding whether to use STN DBS, test patients with FOG to try to predict if surgery has a chance to reduce axial signs of PD, particularly FOG.

4.3. Study limitations

4.3.1. Audio-spinal reflex amplitude

In our controls, ASR was present, but with a lower amplitude (i.e. +25% vs +90%), as compared to previous studies (Delwaide *et al.*, 1993; Pötter *et al.*, 2008). This can be explained by the shorter interval between stimulations: 15 vs 20 to 30 seconds. It is know that ASR is stronger with longer time intervals (Delwaide *et al.*, 1993). We considered longer intervals, but we knew that patients would hardly stay quiet for longer period; risk of movement or sleepiness rises as the experiment prolongs, and could consequently affect Hoffmann's reflex and ASR.

4.3.2. DBS effect on audio-spinal reflex

It had been already shown that both pharmacological (Delwaide *et al.*, 1993) and surgical (Pötter *et al.*, 2008) treatment of PD could increase the amplitude of the ASR. The difference between sessions with DBS ON and OFF was rather small in our study (21%), probably because patients were still on drug therapy (ceiling effect). In this setting, only the incremental effect of STN DBS was assessed. We chose to do so in order to obtain a better

compliance of the subjects. Drop-outs would probably have been more common with drug withdrawal.

4.3.3. Choice of clinical scales

The present study provides a link between electrophysiological data about brainstem and clinical parameters such as gait quality. We only used UPDRS and a FOG questionnaire to assess gait improvement with DBS. FOG questionnaire presents the advantage of scoring gait during a long period (weeks); which is important when dealing with Parkinson's disease and its high daily variability. Nonetheless, we could not compare directly ON and OFF states with this questionnaire. Moreover, FOG questionnaire does not assess all aspects of gait.

A precise scale, aimed at evaluating gait in Parkinson's disease (Crémers *et al.*, 2012), might be used for further investigations, and to compare ON and OFF stimulation conditions.

We did not fill FOG questionnaire OFF stimulation, because it would be necessary to let the patients two whole weeks with DBS switched off. We considered that it was not mandatory, because the purpose was not to assess the effect of DBS on FOG, but rather to evaluate a physiological marker and compare it to gait impairment.

4.3.4. Number of patients

Another limitation of our study resides in the small number of patients tested and the absence of a prospective setting: a further study could assess the evolution over time of gait quality and ASR.

5. Conclusion

This study shows that PD patients, treated by dopaminergic medications and STN DBS, with less FOG, as scored by FOG questionnaire, display a greater increment of ASR induced by STN DBS. Common structures might link this reflex and gait control (reticular nuclei, PPN). This reflex could be a tool to further assess effects of other surgical targets or stimulation parameters on FOG, and should be tested for correlations with other gait scores. It might also be predictive of the probability of FOG after DBS surgery if tested pre-operatively.

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7. Conflicts of interest

None of the authors have potential conflicts of interest to be disclosed.

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