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Modulation of sensory cortical activity by deep brain stimulation in advanced Parkinson's disease

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Abstract

Despite optimal oral drug treatment, about 90% of patients with Parkinson's disease develop motor fluctuation and dyskinesia within 5–10 years from the diagnosis. Moreover, the patients show non-motor symptoms in different sensory domains. Bilateral deep brain stimulation (DBS) applied to the subthalamic nucleus is considered the most effective treatment in advanced Parkinson's disease, and it has been suggested to affect sensorimotor modulation and relate to motor improvement in patients. However, observations on the relationship between sensorimotor activity and clinical improvement have remained sparse. Here, we studied the somatosensory evoked magnetic fields in 13 right-handed patients with advanced Parkinson's disease before and 7 months after stimulator implantation. Somatosensory processing was addressed with magnetoencephalography during alternated median nerve stimulation at both wrists. The strengths and the latencies of the ~60-ms responses at the contralateral primary somatosensory cortices were highly variable but detectable and reliably localized in all patients. The response strengths did not differ between preoperative and postoperative DBS_{ON} measurements. The change in the response strength between preoperative and postoperative condition in the dominant left hemisphere of our right-handed patients correlated with the alleviation of their motor symptoms ($p = .04$). However, the result did not survive correction for multiple comparisons.

Abbreviations: DBS, deep brain stimulation; ECD, equivalent current dipole; LEDD, levodopa equivalent daily dose; MEG, magnetoencephalography; MN, median nerve; OTP, oversampled temporal projection; PD, Parkinson's disease; SEF, somatosensory-evoked magnetic field; SEM, standard error of the mean; SI, primary somatosensory cortices; SII, secondary somatosensory cortices; STN, subthalamic nucleus; tSSS, spatiotemporal signal space separation; UPDRS III, Unified Parkinson's Disease Rating Scale, motor part.

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Magnetoencephalography appears an effective tool to explore non-motor effects in patients with Parkinson's disease, and it may help in understanding the neurophysiological basis of DBS. However, the high interindividual variability in the somatosensory responses and poor tolerability of DBS_{OFF} condition warrants larger patient groups and measurements also in non-medicated patients.

KEYWORDS

deep brain stimulation, magnetoencephalography, non-motor cerebral activity, Parkinson's disease, somatosensory processing

1 | INTRODUCTION

Parkinson's disease (PD) is an age-related progressive neurodegenerative disorder, currently affecting more than six million people worldwide (Dorsey et al., 2018). The clinical symptoms of PD include asymmetrical onset of bradykinesia, rigidity and resting tremor (Groiss et al., 2009). In the advanced PD, patients typically have severe daily motor fluctuations and dyskinesia despite optimal oral medication. Patients may also have severe cognitive deficits and sometimes even psychotic symptoms (Luquin et al., 2017).

Despite optimal oral drug treatment, about 90% of PD patients develop motor fluctuations and/or dyskinesia within 5–10 years from the diagnosis (Manson et al., 2012). The most effective treatment in advanced PD is bilateral deep brain stimulation (DBS) applied to the subthalamic nucleus (STN). STN DBS improves motor symptoms, as assessed by the motor Unified Parkinson's Disease Rating Scale (UPDRS III), in more than 60% of the patients, and reduces dyskinesia and the dose of dopaminergic medications for half of the patients (Deuschl et al., 2006; Krack et al., 2003; Limousin et al., 1998). The physiological basis of the efficacy of STN DBS has remained elusive. DBS has been suggested to restore the normal oscillatory activity in the basal ganglia and thus reduce clinical symptoms (Bergman & Deuschl, 2002). DBS may also modulate neuronal inhibition–excitation balance (Benazzouz et al., 2000; Liu et al., 2008) and cortical networks (Hartmann et al., 2018; Lozano & Lipsman, 2013). DBS inhibits low beta-band activity (~11–14 Hz) at STN, and the level of inhibition correlates with the clinical motor outcome both during (Oswal et al., 2016) and after the stimulation (Bronte-Stewart et al., 2009; Kühn et al., 2008). Furthermore, STN DBS may alleviate PD symptoms by reducing the interplay between the subthalamic beta rhythms and broadband activity associated with rigidity and akinesia (Lozano & Lipsman, 2013).

Although motor symptoms are the hallmark of advanced PD, prominent changes may occur also in various non-motor sensory domains (Cao et al., 2011; Conte et al., 2010; Lee et al., 2005), particularly in proprioception and sensorimotor integration (Abbruzzese & Beradelli, 2003). Furthermore, PD patients can have cognitive deficits, for example, in verbal fluency (Højlund et al., 2017) and neuropsychiatric symptoms (Voon et al., 2006).

Results of STN DBS on somatosensory processing have been mixed. Whereas STN DBS has been demonstrated to worsen somatosensory temporal discrimination (Conte et al., 2010), it reduces the threshold of two-point discrimination in PD patients, thus improving somatosensory processing (Huzmeli et al., 2020). STN DBS has been suggested to improve proprioception in PD patients by initiation of more stable neuronal firing within the basal ganglia (Aman et al., 2014) and by affecting afferent information processing within sensory pathways and thus normalizing functions related to sensorimotor integration (Sailer et al., 2003; Shukla et al., 2013).

Magnetoencephalography (MEG) provides a non-invasive and patient-friendly method for characterizing complex neural functions in space and time. STN DBS activates the somatosensory cortex within 1 ms after the electric pulse is applied via the DBS electrode, demonstrated with both MEG (Hartmann et al., 2018) and EEG (Walker et al., 2012) recordings. This fast response is probably mediated via antidromic activation of hyperdirect cortico-subcortical fibres adjacent to the DBS electrode, succeeded by later orthodromic activations (Miocinovic et al., 2018). Both experimental PD models (Gradinaru et al., 2009) and previous MEG studies on PD patients (Airaksinen et al., 2011; Cao et al., 2017; Hartmann et al., 2018; Sridharan et al., 2017) have suggested that STN DBS may modulate sensorimotor processing in PD patients and, by improving sensorimotor integration, enhance motor performance. However, observations on correlations between sensorimotor

activity and clinical improvement have remained sparse. No data of the long-term effects of DBS on somatosensory-evoked fields (SEFs) from the primary somatosensory cortex (SI), in comparison with preoperative SEFs, are available.

Secondary somatosensory cortex (SII) is located in the parietal operculum of the upper lip of the Sylvian fissure, and it contributes to sensorimotor integration (for a recent review, see Bretas et al., 2020). Somatosensory stimulation elicits MEG responses in SII, and they can easily be separated from the activation of the SI (for a review, see Hari & Forss, 1999). Signals recorded directly from DBS electrodes implanted in STN are coherent with spontaneous alpha band activity measured by MEG from the temporoparietal regions (Hirschmann et al., 2011; Litvak et al., 2011). Thus, DBS may be involved in modulating activity at the SII region. Possible effects of DBS on SII responses have not been reported previously.

In this exploratory study, we addressed the possible long-term changes related to STN DBS in the somatosensory cortices of advanced PD patients using MEG. Median nerve (MN) stimulation at both wrists, a clinically and research-wise well-established and replicable way to study somatosensory cortex function (e.g., Nenonen et al., 2010), was used to evoke SEFs. We studied the SEFs through successive measurements at ~6 months before and at ~7 months after DBS implantation and assessed the possible correlations of SEFs with the patients' motor outcome.

2 | MATERIALS AND METHODS

2.1 | Subjects

Sixteen advanced PD patients were studied before (6 ± 0.8 months; mean \pm SEM) and after (7 ± 0.4 months) the implantation of bilateral STN DBS (Activa PC, Medtronic) with both DBS on and off. All patients had electrodes with four contacts, and the space between the contacts inserted to STN was 0.5 mm. The timing of the postoperative MEG measurement depended on the postoperative out-patient visit for check-up and possible adjustment of DBS stimulus parameters; exact timing of these assessments varied slightly.

Three patients had to be excluded from further analysis due to inappropriate data quality related to the artefacts produced by the DBS stimulation. The age of the remaining 13 patients (10 men, three women) was 55 ± 9 years, and the time from the PD diagnosis to DBS implementation was 13 ± 5 years. All subjects were right-handed by self-report. The patients are described in detail in Table 1. All patients were clinically stable and

used their normal anti-Parkinsonian medication during the MEG measurements.

The motor assessments were based on UPDRS III scores, conducted independently from the MEG measurements by an experienced movement disorder neurologist immediately after the MEG sessions.

The experiment was accepted by the Helsinki University Hospital Ethical Committee, and all patients gave their written informed consent to participate.

2.2 | Measurements

The measurements were conducted with a 306-channel whole-head Vectorview neuromagnetometer (Elekta Oy, Finland) in a magnetically shielded room (Euroshield, Finland). An experienced nurse was present in the shielded room during measurements to ensure the well-being of the patient.

In the following notation, preoperative condition (PRE) will refer to the clinical assessment and MEG measurements done before the DBS implantation, and DBS_{ON} or DBS_{OFF} will refer to the measurements conducted after the DBS implantation (DBS either on or off). Postoperative MEG measurements were conducted on the same day, with DBS_{ON} always preceding DBS_{OFF}. In DBS_{OFF}, positioning of the PD patients under the MEG device is often uncomfortable due to rigidity; therefore, the order of recordings (on vs. off) was not counterbalanced across patients. The recordings were conducted with a short (10 min) pause between the measurements, as most patients do not tolerate well the DBS_{OFF} state.

The SEFs were elicited by 200- μ s square wave pulses, delivered alternately to the MN at both wrists with a stimulation strength that was not painful but produced a stable and visible thumb twitch. The stimuli were presented within a multimodal stimulation paradigm consisting of auditory, somatosensory and visual stimuli applied with mean interstimulus interval of 5.5 s between stimuli within any single modality. The stimuli were presented in a random order. This multimodal stimulation has been previously used to study the effects of DBS on and off on SEFs and auditory evoked fields (AEFs; Airaksinen et al., 2011). Moreover, SEFs elicited by this stimulus paradigm have been demonstrated to show excellent replicability in strength and source location across multiple MEG recordings over 6 years, although the exact location of the MN electrodes at wrists may vary slightly across measurement sessions (Nenonen et al., 2010). The present follow-up AEF results are published elsewhere (Valkonen et al., 2022). The visual stimuli were added to increase interstimulus interval between

TABLE 1 Clinical details of patients and their DBS parameters

| № | Sex, DBS op (age) | Handedness | PD duration before op (yr) | MEG measurements | | Levodopa equivalent daily dose (LEDD, mg) ^a | | UPDRS III total scale (medication on) | | DBS settings (left/right) | | | |
|----|-------------------|------------|----------------------------|--------------------|-------------------|--|-------------------|---------------------------------------|-------------------|---------------------------|-------------------------|-----------|------------------|
| | | | | Before DBS op (mo) | After DBS op (mo) | PRE | DBS _{ON} | PRE | DBS _{ON} | Voltage (V) | Type (bi- or monopolar) | Freq (Hz) | Pulse width (µs) |
| 1 | F, 63 | R | 24 | 5 | 7 | 960 | 760 | 32 | 35 | 3.6/1.6 | Bi/bi | 160 | 60/60 |
| 2 | M, 57 | R | 15 | 11 | 6 | 1,618 | 1,310 | 32 | 21 | 2.5/2.5 | Mono/bi | 130 | 60/60 |
| 3 | M, 63 | R | 8 | 3 | 7 | 925 | 639 | 37 | 29 | 2.5/2.5 | Mono/mono | 160 | 60/60 |
| 4 | M, 62 | R | 17 | 8 | 5 | 1,408 | 1,407 | 37 | 33 | 3.6/3.1 | Mono/mono | 130 | 60/60 |
| 5 | M, 42 | R | 9 | 3 | 6 | 765 | 1,497 | 62 | 32 | 3.2/3.2 | Mono/mono | 130 | 60/60 |
| 6 | M, 49 | R | 14 | 8 | 11 | 1,263 | 1,105 | 51 | 24 | 3.5/3.1 | Bi/mono | 150 | 60/60 |
| 7 | M, 42 | R | 6 | 5 | 6 | 1,338 | 1,360 | 44 | 20 | 3.5/2.0 | Mono/mono | 130 | 60/60 |
| 8 | M, 62 | R | 18 | 4 | 7 | 1,158 | 560 | 27 | 20 | 2.9/3.0 | Mono/mono | 130 | 60/60 |
| 9 | F, 63 | R | 14 | 9 | 7 | 658 | 366 | 23 | 16 | 2.8/2.9 | Mono/mono | 130 | 60/60 |
| 10 | F, 56 | R | 18 | 0.5 | 7 | 1,562 | 1,386 | 74 | 34 | 2.6/2.7 | Mono/mono | 130 | 60/60 |
| 11 | M, 67 | R | 9 | 5 | 7 | 1,679 | 480 | 46 | 25 | 2.6/2.9 | Mono/mono | 150 | 120/60 |
| 12 | M, 45 | R | 9 | 5 | 5 | 1,481 | 1,255 | 31 | 29 | 3.5/3.8 | Bi/mono | 130 | 60/60 |
| 13 | M, 47 | R | 8 | 3 | 6 | 655 | 580 | 37 | 24 | 2.3/2.5 | Mono/mono | 180 | 60/60 |

Abbreviations: DBS, deep brain stimulation; DBS_{ON}, deep brain stimulation on; F, female; Freq., frequency; LEDD, levodopa equivalent daily dose; M, male; mo, months; op, DBS operation; PD, Parkinson's disease; PRE, preoperative condition; UPDRS III scale, Unified Parkinson's Disease Rating Scale; yr, years.

^aTo calculate the levodopa equivalent daily dose (LEDD), the following formula was used: 100 mg l-dopa = 130 mg controlled-release l-dopa = 70 mg l-dopa + COMT inhibitor = 1 mg pramipexole = 5 mg ropinirole = 4 mg rotigotine.

SEFs and AEFs and to add variability to the stimulation. They were not constructed in a manner to be analysed. In our study, the SEF responses were compared on average 13 months apart.

The exact head coordinates and their position with respect to the sensor array were measured before measurements by feeding a short current pulse to four head position indicator. HPI was measured before the DBS_{ON} condition, and the HPI coil frequencies were adjusted to avoid possible interference with the DBS; continuous HPI was not available. For adjustment of MEG and magnetic resonance imaging head coordinates, the position of the coils relative to the head landmarks was determined with a 3-D digitizer (Fastrak[®], Polhemus, Inc., Colchester, Vermont, United States).

2.3 | Data processing

In addition to the artefacts caused by the DBS and its related harmonics, external artefacts induced by the impulse generator and implanted wires moving close to the MEG sensors are present in the MEG raw data. Spatiotemporal signal space separation (tSSS) (Taulu & Simola, 2006) algorithm, implemented in MaxFilter software (Elekta Neuromag), was employed for artefact removal. In tSSS, the measured signal is first divided into two subspaces, that is, internal signal from the sensory array, and external signal originating outside the helmet. After the division, temporally correlated components between the subspaces, such as those related to DBS, are recognized by principal component analysis and removed from the data (Taulu & Simola, 2006). The original brain signals are so weak that they do not expand to the external source space and thus remain intact (Taulu & Simola, 2006). The effect of tSSS on the MEG signals used in averaging the AEFs and SEFs has been visualized and discussed in Airaksinen et al. (2011) and proven effective in previous studies (Airaksinen et al., 2011; Cao et al., 2015).

The tSSS time window was set to 10 s, and the subspace correlation limit to .9. To further improve signal-to-noise ratio, oversampled temporal projection (OTP) (Larson & Taulu, 2018) was applied before tSSS for suppressing spatially noncorrelated sensor noise. Remaining artefacts and spikes were filtered out by applying low-pass filtering at 90 Hz. For one patient, additional high-pass filtering at 10 Hz was applied similarly in all experimental conditions due to remaining low-frequency artefacts, resulting in a typical SEF waveform (Airaksinen et al., 2011).

Subsequently, the responses were averaged from 100 ms before stimulus onset to 500 ms after it using the

MNE-Python open-source software package (Gramfort et al., 2013). Baseline was determined as the interval from -100 to -5 ms relative to stimulus onset and subtracted from the response.

2.4 | Source-level analysis

For source-space analysis, the head was modelled as a homogeneous sphere. The model parameters were optimized for the intracranial space based on individual head magnetic resonance (MR) images that were available for all subjects. The sources of the responses were modelled with equivalent current dipoles (ECDs) (Hämäläinen et al., 1993), where the model parameters of an ECD represent the location, orientation and strength of the net current in an activated brain area.

SEFs at both primary somatosensory cortices (SI) and secondary somatosensory cortices (SII) were explored in the current study. Responses at the contralateral primary somatosensory cortices (SI) were identified using 12–16 gradiometer pairs located in the area of the strongest response at the time period of 20–85 ms after stimulus onset, for both left- and right-sided MN stimulations. To add confidence to the source estimates, we did the SI source modelling of the 60-ms responses, as they were the most prominent (and thus least noise sensitive). For other SEFs (e.g., N20m), it was not always feasible to find a clear response peak, and we concentrated on responses that were reliably available in all subjects.

Responses at the secondary somatosensory cortices (SII) were identified using 12–16 gradiometer pairs located in the area of the strongest response over the parietotemporal cortex at the time period 85–140 ms after the stimulus onset. Contralateral SII responses were detected in nine out of 13 subjects, resulting in two-dipole models per hemisphere for fully explaining the measured magnetic fields to left- and right-sided MN stimulations. In one patient, a third dipole was needed to model additional activity at both hemispheres.

The cortical sources underlying the measured SEFs were first separately found for each experimental condition (left vs. right stimulation, PRE, DBS_{ON}); DBS_{OFF} condition was not used for source localization as the data was available only in nine out of 13 patients. We postulated that the locations of the SEFs would not change among the experimental conditions; that is, DBS does not change cortical response locations. Thus, in all patients, the strongest (and thus least noise sensitive) source per hemisphere was selected over the experimental conditions and applied in the other conditions. The selected sources were stable in time over tens of milliseconds, and they explained more than 75% of the local field variance

during the response peaks at the selected channels. The ECDs were then fixed in space and allowed to change in time and amplitude to best explain the signals over all sensors. The peak latencies and maximum source strengths were detected from the obtained dipole strength versus time curves and compared between the conditions.

To examine the possible relationship between the SEFs and the clinical outcome in PD patients, the relative change of source strengths between preoperative and postoperative MEG measurements and relative change in patient's motor performance was calculated as follows:

$$\left(\text{PRE}_{(\text{source strength})} - \text{DBS}_{\text{ON}(\text{source strength})} \right) / \text{PRE}_{(\text{source strength})}$$

= Relative change in source strengths between DBS_{ON} and PRE conditions.

Similarly, the relative change in UPDRS III total motor score was obtained in the DBS_{ON} condition, as the patients were in medication on state:

$$\left(\text{PRE}_{(\text{total UPDRS III motor score})} - \text{DBS}_{\text{ON}(\text{total UPDRS III motor score})} \right) / \text{PRE}_{(\text{total UPDRS III motor score})}$$

2.5 | Statistical analysis

The data were first checked for normal distribution and equality of variances with Shapiro–Wilk's and Levene's tests. To assess the differences in source strengths and latencies between the different experimental conditions, repeated measures analysis of variance (ANOVA) was applied. For addressing the possible correlations between changes in the SEFs and clinical outcomes in UPDRS III total scale, Spearman's rank correlation (r_s) was introduced. Statistical significance level of .025 was considered significant (corrected over comparisons over two hemispheres).

3 | RESULTS

Motor symptoms were effectively relieved by DBS in most patients: the mean scores for UPDRS III total scale (in absolute values; mean \pm SEM) reduced from 41 ± 4 (PRE) to 26 ± 2 (DBS_{ON}; $p < .05$), although the patients were on medication (average change in UPDRS III between the two conditions 15 ± 4). Simultaneously, the levodopa equivalent daily dose (LEDD) used by the patients appeared to reduce from $1,190 \pm 101$ mg (PRE) to 977 ± 116 mg (DBS_{ON}), with average change of 201 ± 118 mg (n.s.).

The SEFs to right MN stimulation in one PD patient and the corresponding ECD used to model the SI responses are shown in Figure 1. The responses were prominent with small variability at the single-trial level (see insert, Figure 1). The cortical activity localized in the SI cortex posterior to the central sulcus, peaked at 28, 38 and 70 ms after the stimulation. At the group level, the right SI cortical activity across the conditions (to the left MN stimulation) peaked at (mean \pm SEM) 36 ± 1 ms, at 51 ± 2 ms, and at 98 ± 3 ms; the corresponding deflections at the left SI (for right MN stimulation) were observed at 38 ± 2 ms, at 53 ± 2 ms, and at 95 ± 3 ms. The strongest SI activity was observed at 51 ± 2 ms in the right hemisphere and at 53 ± 2 ms in the left hemisphere, corresponding to the P60m response described in the literature (Airaksinen et al., 2011; Hari & Forss, 1999; Hartmann et al., 2018).

The 60-ms SI responses were reliably localized in both hemispheres in all patients in preoperative and DBS_{ON} conditions (see Figure S1 for the individual responses in all subjects). The responses were highly individual but consistent at the individual level in the successive measurements separated by ~ 7 months.

Table 2 summarizes the maximum source strengths for SI responses in both hemispheres and for PRE, DBS_{ON} and DBS_{OFF} conditions. As four out of 13 patients did not tolerate the DBS_{OFF} measurements, and SII response were detectable in only nine patients, the statistical analysis were conducted only between the PRE and DBS_{ON} conditions on SI responses. The mean source strengths and peak latencies of the SII responses are presented in Table S1. The variation in the source strengths was substantial between patients and hemispheres, and there were no statistically significant differences between the experimental conditions for neither source strengths nor latencies. The change of UPDRS III total motor score appeared to correlate negatively with the change of SI response source strength between PRE and DBS_{ON} conditions in the left hemisphere, dominant for handedness ($r_s = -.58$, $p = .04$; Figure 2): strong alleviation of motor symptoms by DBS (reduction of UPDRS III total score) was related to strong increase in the SI source strength. However, this result did not survive correction for multiple comparisons. Similar comparison on the right-hemispheric SI responses remained non-significant ($r_s = -.02$, $p = .96$).

4 | DISCUSSION

Our results demonstrate that with careful artefact management, responses at the primary somatosensory cortices in PD patients with DBS can be reliably addressed

FIGURE 1 Somatosensory responses induced by the right-sided median nerve (MN) stimulation in one patient. Top: Sensor-level data; the insert depicts the left hemisphere channels with maximum response amplitude and the single-trial responses at one channel (red = mean over 166 single-trial responses, blue = ± 1 SD). Bottom: The equivalent current dipole (ECD) location and orientation superimposed on the patient's magnetic resonance (MR) image (left) and strength of the ECD as a function of time (black = PRE, red = DBS_{ON}). Note: The stimulus artefacts are present at the 0-ms time point

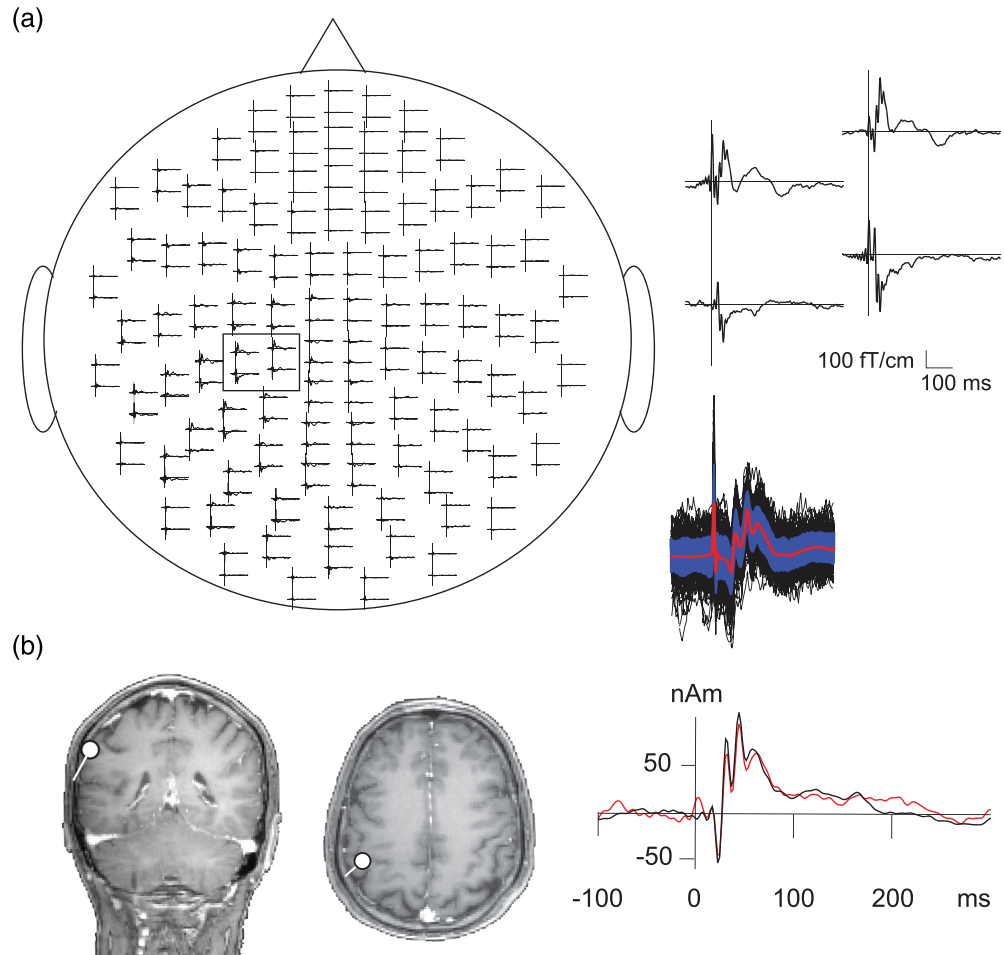


TABLE 2 SI source strengths (mean \pm SEM)

| Condition | Source strengths (nAm) ^a | |
|---|-------------------------------------|------------------|
| | Left hemisphere | Right hemisphere |
| PRE ($N = 13$) | 46 \pm 8 | 52 \pm 8 |
| DBS _{ON} ($N = 13$) | 36 \pm 7 | 52 \pm 9 |
| DBS _{OFF} ($N = 9$ /LH, 8/RH) | 35 \pm 8 | 49 \pm 10 |

^aThe peak strength of the filtered response.

Abbreviations: DBS_{OFF}, deep brain stimulation off; DBS_{ON}, deep brain stimulation on; LH, left hemisphere; PRE, preoperative condition; RH, right hemisphere.

over several months with MEG, for studying possible long-term effects of the stimulation. DBS may be involved in the modulation of sensorimotor integration in advanced PD patients, with suggestive correlation of the SI cortex responses of the dominant left hemisphere and the DBS-induced improvement of motor symptoms as indexed by UPDRS III assessment. However, additional studies with larger patient groups are needed.

The clinical improvement of our advanced PD patients with DBS is consistent with previous findings

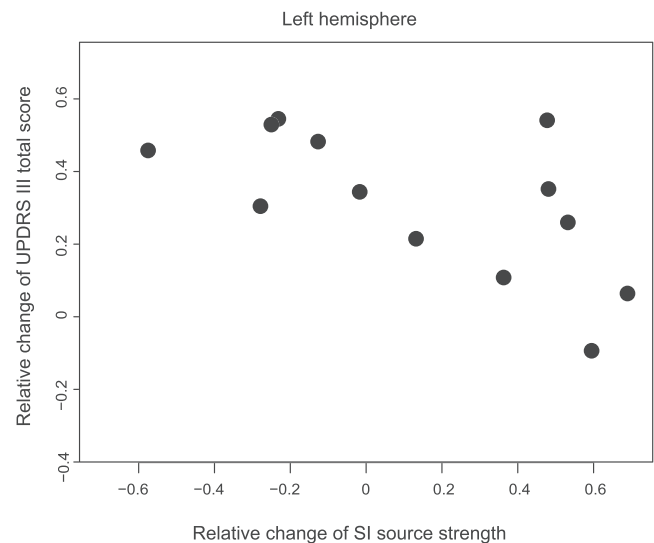


FIGURE 2 Scatter plot of the relative change of SI source strength between preoperative and DBS_{ON} condition and relative change of Unified Parkinson's Disease Rating Scale (UPDRS III) total motor score ($r_s[13] = -.58$, $p = .04$)

(Benabid et al., 2009; Deuschl et al., 2006; Groiss et al., 2009; Krack et al., 2003; Limousin et al., 1998; Mostofi et al., 2019; Mueller et al., 2018). The motor

system is controlled by continuous somatosensory feedback from joints and muscles and pathological changes in the feedback are likely to deteriorate motor performance in PD patients. DBS-induced changes in sensorimotor integration have earlier been related to motor improvement in PD patients (Shukla et al., 2018). The observed suggestive correlation of change in 60-ms SEF strength with motor improvement in the present study speaks for a possible link between DBS and sensorimotor integrative processing even after the thalamocortical input to sensory cortices at about 20 ms after the stimulus. Our exploratory data of SII responses demonstrate the feasibility of addressing also these responses with MEG over time in PD patients, but more data are needed for evaluating their role in the possible DBS-induced changes of sensorimotor integration.

PD itself is known to modify somatosensory evoked responses. The deflection at 30 ms (N30) in somatosensory-evoked potentials (SEPs) has been reported to be suppressed in PD (Rossini et al., 1989) and enhanced by levodopa treatment (Miranda et al., 1996; Rossini et al., 1989). Furthermore, although the magnetic 20-ms responses (N20m) are similar to controls, the N60m response has been reported to be significantly delayed in PD (Mäkelä et al., 1993). The earlier reports on the effects of STN DBS on somatosensory evoked responses have been variable. STN and globus pallidus pars interna (GPI) DBS have been reported to both enhance SEPs at 20 and 30 ms (Insola et al., 2005; Pierantozzi et al., 1999) and to diminish them (Priori et al., 2001), whereas earlier MEG recordings did not find significant changes in the N20m nor P60m responses (Airaksinen et al., 2011; Sridharan et al., 2017); changes in the response latencies by DBS have not been reported. In line with the previous results, we did not observe differences in SEF latencies, nor in the absolute source strengths between DBS on and off conditions despite our improved artefact management (Larson & Taulu, 2018).

We could not make reliable observations between the cortical DBS_{OFF} measures and clinical outcome because we had DBS_{OFF} data only from nine patients. Furthermore, we could not fully exclude the effect of DBS wash-out period on the DBS off responses, as the patients were measured after only 10 min since turning the DBS off. At least 3 h of STN DBS off is required to establish a steady motor DBS off state for efficacy studies (Temperli et al., 2003), although 50% of the total change in the motor scales has been estimated to occur within first 5 min after DBS is turned off (Little et al., 2013). When the DBS is turned on, tremor and rigidity start to improve in minutes, whereas improvements in bradykinesia may take weeks and changes in mood or dystonia take

months (Ashkan et al., 2017). Further studies with larger patient group and with longer DBS_{OFF} times will be required to find out the possible long-term cortical reorganization induced by the treatment.

Another limitation of the current study is that all our patients were on medication during the MEG measurements. However, it is unlikely that our potential correlation of patients' clinical improvement and increase in the strength of SI response would be related to anti-Parkinsonian medication, as there was no significant change in the LEDDs between preoperative and postoperative conditions; LEDDs decreased or remained the same in 11 out of our 13 patients after the operation. Further studies should address medication off patients for distinguishing the effect of STN DBS and dopaminergic medication on SEFs.

Our present results support the previous findings (Airaksinen et al., 2011; Hartmann et al., 2018; Litvak et al., 2012, 2011) that MEG can be successfully applied to study the neurophysiological effects of DBS despite the prominent stimulator-related magnetic artefacts and that the tSSS method applied to suppress the artefacts does not appear to affect the actual brain electrophysiological activity (Boring et al., 2019). In the future, novel directional electrodes may decrease the measurement artefacts (Hell et al., 2019; Shao et al., 2019) and thus increase the usability of MEG in addressing cortical changes in PD patients. Our results indicate a possible correlation between change in SI response strength in the dominant hemisphere (determined by handedness) and clinical outcome. At the time of the measurements, most patients had bilateral symptoms, and the hemisphere affected first by PD was not always clearly defined. In the future studies on cortical somatosensory processing, the laterality of the patients' symptom profile should also be taken into account.

5 | CONCLUSION

The possible modulations of cortical somatosensory processing induced by STN DBS can be reliably studied over months in advanced PD patients with MEG but require careful artefact removal. Our present results suggest that changes in the source strengths at the dominant SI cortex between preoperative and DBS conditions may correlate with the patients' motor improvement induced by DBS. However, further studies with larger sample sizes, in DBS_{OFF} and medication off conditions, as well as by taking into account the laterality of patients' symptom profile, are needed to shed more light on the DBS-induced changes in advanced PD.

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CONFLICTS OF INTEREST

Eero Pekkonen is a consulting neurologist for Finnish Patient Insurance Centre, and a member of the MDS Non-Motor Parkinson's Disease Study Group. He is a Person Responsible of Trial in Finland: International Adroitstudy, 2021-, organized by Abbott. He is a member of advisory board of Abbvie. He has received consulting fees from NordicInfu Care AB, Abbvie, lecture fees from Abbott, Abbvie, NordicInfu Care. Other authors reported no financial interests and potential conflict of interests.

ETHICS STATEMENT

The study was accepted by the Helsinki University Hospital Ethical Committee (HUS/163/2019), and all patients gave their informed written consent.

AUTHOR CONTRIBUTIONS

Olesia Korsun: formal analysis, writing - original draft, visualization and funding acquisition. **Hanna Renvall:** supervision, writing - review & editing, visualization and funding acquisition. **Jussi Nurminen:** software and data curation. **Jyrki P. Mäkelä:** supervision, conceptualization and writing - review & editing. **Eero Pekkonen:** supervision, conceptualization, patient recruitment and writing - review & editing.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/ejn.15692>.

DATA AVAILABILITY STATEMENT

The original datasets are not publicly available due to restrictions placed by the Helsinki University Hospital Research Ethics Committee. The data that support the findings of this study are available from the corresponding author with permission of the Helsinki University Hospital Research Ethics Committee.

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